schedule and route of vaccine administration. Of those, 28 were enrolled into the study arm to receive the licensed schedule (initial injections at 0, 2 and 4 weeks followed by additional doses at 6, 12 and 18 months) and were subsequently monitored for the occurrence of local and systemic adverse events. (See ADVERSE REACTIONS)

INDICATIONS AND USAGE

BioThrax is indicated for the active immunization against *Bacillus anthracis* of individuals between 18 and 65 years of age who come in contact with animal products such as hides, hair or bones that come from anthrax endemic areas, and that may be contaminated with *Bacillus anthracis* spores. BioThrax is also indicated for individuals at high risk of exposure to *Bacillus anthracis* spores such as veterinarians, laboratory workers and others whose occupation may involve handling potentially infected animals or other contaminated materials.

Since the risk of anthrax infection in the general population is low, routine immunization is not recommended.

The safety and efficacy of BioThrax in a post-exposure setting has not been established.

CONTRAINDICATIONS

The use of BioThrax is contraindicated in subjects with a history of anaphylactic or anaphylactic-like reaction following a previous dose of BioThrax, or any of the vaccine components.

WARNINGS

Preliminary results of a recent unpublished retrospective study of infants born to women in the U.S. military service worldwide in 1998 and 1999 suggest that the vaccine may be linked with an increase in the number of birth defects when given during pregnancy (unpublished data, Department of Defense). Although these data are unconfirmed, pregnant women should not be vaccinated against anthrax unless the potential benefits of vaccination have been determined to outweigh the potential risk to the fetus.

Animal reproduction studies have not been conducted with BioThrax.

PRECAUTIONS

Before administration, the patient's medical immunization history should be reviewed for possible vaccine sensitivities and/or previous vaccination-related adverse events, in order to determine the existence of any contraindications to immunization.

Pregnant women should not be vaccinated against anthrax unless the potential benefits of vaccination clearly outweigh the potential risks to the fetus.

BioThrax should not be administered to individuals with a history of Guillain-Barré Syndrome (GBS) unless there is a clear benefit that outweighs the potential risk of a recurrence.

History of anthrax disease may increase the potential for severe local adverse reactions.

Patients with impaired immune responsiveness due to congenital or acquired immunodeficiency, or immunosuppressive therapy may not be adequately immunized following administration of BioThrax. Vaccination during chemotherapy, high dose corticosteroid therapy of greater than 2-week duration, or radiation therapy may result in a suboptimal response. Deferral of vaccination for 3 months after completion of such therapy may be considered.[7]

The administration of BioThrax to persons with concurrent moderate or severe illness should be postponed until recovery. Vaccination is not contraindicated in subjects with mild illnesses with or without low-grade fever.[7]

This product should be administered with caution to patients with a possible history of latex sensitivity since the vial stopper contains dry natural rubber.

Epinephrine solution, 1:1000, should always be available for immediate use in case an anaphylactic reaction should occur.

Pregnancy
PREGNANCY CATEGORY D.
See Warnings.

Nursing Mothers
It is not known whether exposure of the mother to BioThrax poses a risk of harm to the breast-feeding child. However, administration of non-live vaccines (e.g., anthrax vaccine) during breast-feeding is not medically contraindicated.[7]

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
No data regarding the safety of BioThrax are available for persons aged > 65 years.

ADVERSE REACTIONS

Pre Licensure
Local Reactions- In an open-label safety study, 15,907 doses of BioThrax were administered to approximately 7,000 textile employees, laboratory workers and other at risk individuals *(See Clinical Studies)*. Over the course of the 5-year study, there were 24 reports (0.15% of doses administered) of severe local reactions (defined as edema or induration measuring greater than 120 mm in diameter or accompanied by marked limitation of arm motion or marked axillary node tenderness). There were 150 reports (0.94% of doses administered) of moderate local reactions (edema or induration greater than 30 mm but less than 120 mm in diameter) and 1373 reports (8.63% of doses administered) of mild local reactions (erythema only or induration measuring less than 30 mm in diameter).

Systemic Reactions- In the same open label study, four cases of systemic reactions were reported during a five-year reporting period (<0.06% of doses administered). These reactions, which were reported to have been transient, included fever, chills, nausea and general body aches.

Post Licensure

Recently (1996-1999), an assessment of safety was conducted as part of a randomized clinical study conducted by the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) *(See Clinical Studies)*. A total of 28 volunteers were enrolled to receive subcutaneous doses of BioThrax according to the licensed schedule. Each volunteer was observed for approximately 30 minutes after administration of AVA and scheduled for follow-up evaluations at 1-3 days, 1 week and 1 month after vaccination. Four volunteers reported seven acute adverse events within 30 minutes after the subcutaneous administration of BioThrax. These included erythema (3), headache (2), fever (1) and elevated temperature (1). Of these events, a single patient reported the simultaneous occurrence of headache, fever and elevated temperature (100.7°F).

Local Reactions- The most common local reactions reported after the first dose (n=28) in this study were tenderness (71%), erythema (43%), subcutaneous nodule (36%), induration (21%), warmth (11%) and local pruritus (7%). The most frequently reported local reactions after the second dose (n=28) were tenderness (61%), subcutaneous nodule (39%), erythema (32%), induration (18%), local pruritus (14%), warmth (11%) and arm motion limitation (7%). After the third dose (n=26), the most frequently reported local reactions were tenderness (58%), warmth (19%), local pruritis (19%), erythema (12%), arm motion limitation (12%), induration (8%), edema (8%) and subcutaneous nodule (4%). Local reactions were found to occur more often in women. No abscess or necrosis was observed at the injection site.

Systemic Reactions- All systemic adverse events reported in this study were transient in nature. The systemic reactions most frequently reported after the first dose (n=28) were headache (7%), respiratory difficulty (4%) and fever (4%). After the second dose (n=28), the most frequently reported systemic reactions were malaise (11%), myalgia (7%), fever (7%), headache (4%), anorexia (4%) and nausea or vomiting (4%). After the third dose (n=26), the most frequently reported systemic reactions were headache (4%), malaise (4%), myalgia (4%) and fever (4%). There was one report of delayed hypersensitivity reaction beginning with lesions 3 days after the first dose. The subject was reported to have diffuse hives by day 17, 3 days after the second dose, and had swollen hands, face and feet by day 18 and discomfort swallowing. The subject did not receive any subsequent scheduled doses.

Post Licensure Adverse Event Surveillance

Data regarding potential adverse events following anthrax vaccination are available from the Vaccine Adverse Event Reporting System (VAERS).[8] The report of an adverse event to VAERS is not proof that a vaccine caused the event. Because of the limitations of spontaneous reporting systems, determining causality for specific types of adverse events, with the exception of injection-site reactions, is often not possible using VAERS data alone. The following four paragraphs describe spontaneous reports of adverse events, without regard to causality.

From 1990 to October 2001, over 2 million doses of BioThrax have been administered in the United States. Through October 2001, VAERS received approximately 1850 spontaneous reports of adverse events. The most frequently reported adverse events were erythema, headache, arthralgia, fatigue, fever, peripheral swelling, pruritus, nausea, injection site edema, pain/tenderness and dizziness.

Approximately 6% of the reported events were listed as serious. Serious adverse events include those that result in death, hospitalization, permanent disability or are life-threatening. The serious adverse events most frequently reported were in the following body system categories: general disorders and administration site conditions, nervous system disorders, skin and subcutaneous tissue disorders, and musculoskeletal, connective tissue and bone disorders. Anaphylaxis and/or other generalized hypersensitivity reactions, as well as serious local reactions, were reported to occur occasionally following administration of BioThrax. None of these hypersensitivity reactions have been fatal.

Other infrequently reported serious adverse events that have occurred in persons who have received BioThrax have included: cellulitis, cysts, pemphigus vulgaris, endocarditis, sepsis, angioedema and

other hypersensitivity reactions, asthma, aplastic anemia, neutropenia, idiopathic thrombocytopenia purpura, lymphoma, leukemia, collagen vascular disease, systemic lupus erythematosus, multiple sclerosis, polyarteritis nodosa, inflammatory arthritis, transverse myelitis, Guillain-Barré Syndrome, immune deficiency, seizure, mental status changes, psychiatric disorders, tremors, cerebrovascular accident (CVA), facial palsy, hearing and visual disorders, aseptic meningitis, encephalitis, myocarditis, cardiomyopathy, atrial fibrillation, syncope, glomerulonephritis, renal failure, spontaneous abortion and liver abscess. Infrequent reports were also received of multisystem disorders defined as chronic symptoms involving at least two of the following three categories: fatigue, mood-cognition, musculoskeletal system.

Reports of fatalities included sudden cardiac arrest (2), myocardial infarction with polyarteritis nodosa (1), aplastic anemia (1), suicide (1) and central nervous system (CNS) lymphoma (1).

Post Licensure Survey Studies

In addition to the VAERS data, adverse events following anthrax vaccination have been assessed in survey studies conducted by the Department of Defense in the context of their anthrax vaccination program. These survey studies are subject to several methodological limitations, e.g., sample size, the limited ability to detect adverse events, observational bias, loss to follow-up, exemption of vaccine recipients with previous adverse events and the absence of unvaccinated control groups. Overall, the most reported events were localized, minor and self-limited and included muscle or joint aches, headache and fatigue. Across these studies, systemic reactions were reported in 5-35% of vaccine recipients and included reports of malaise, chills, rashes, headaches and low-grade fever. Women reported these symptoms more often than men.

Reporting Adverse Events

Adverse events following immunization with BioThrax should be reported to the Medical Affairs Division of BioPort Corporation (517) 327-1675 during regular working hours and (517) 327-7200 during off hours. Adverse events may also be reported to the U. S. Department of Health and Human Services (DHHS) Vaccine Adverse Event Reporting System. Report forms and reporting requirement information can be obtained from VAERS through a toll free number 1-800-822-7967.

DOSAGE AND ADMINISTRATION

Dosage

Immunization consists of three subcutaneous injections, 0.5 mL each, given 2 weeks apart followed by three additional subcutaneous injections, 0.5 mL each, given at 6, 12, and 18 months. Subsequent booster injections of 0.5 mL of BioThrax at one-year intervals are recommended.

Administration

Use a separate 5/8-inch, 25- to 27-gauge sterile needle and syringe for each patient to avoid transmission of viral hepatitis and other infectious agents. Use a different site for each sequential injection of this vaccine and do not mix with any other product in the syringe.

1. Shake the bottle thoroughly to ensure that the suspension is homogeneous during withdrawal and visually inspect the product for particulate matter and discoloration. If the product appears discolored or has visible particulate matter, DISCARD THE VIAL.
2. Wipe the rubber stopper with an alcohol swab and allow to dry before inserting the needle.
3. Clean the area to be injected with an alcohol swab or other suitable antiseptic.
4. Holding the needle at a 45° angle to the skin, inject the vaccine subcutaneously.
5. DO NOT inject the product intravenously. Follow the usual precautions to ensure that you have not entered a vein before injecting the vaccine.
6. After injecting, withdraw the needle and briefly and gently massage the injection site to promote dispersal of the vaccine.

HOW SUPPLIED/STORAGE
Anthrax Vaccine Adsorbed (BioThrax™) is supplied in 5 mL multidose vials.

THIS PRODUCT IS TO BE STORED AT 2°C TO 8°C (36 TO 46°F). Do not freeze. Do not use after the expiration date given on the package.

Nonclinical Toxicology
Carcinogenesis, Mutagenesis, Impairment of Fertility
Animal studies have not been performed to ascertain whether BioThrax has carcinogenic action, or any effect on fertility.

REFERENCES

1. Meselson, M., et al., 1994. The Sverdlosk anthrax outbreak of 1979. *Science* 266:1201-8.
2. Henderson, D.W., Peacock, S., Belton, F.C., 1956. Observations on the prophylaxis of experimental pulmonary anthrax in the monkey. *J. Hygiene*, 54:28-36.
3. Brachman, P.S., 1980. Inhalation Anthrax. *Ann. NY Acad. Science*, 353:83-93.
4. Update: Investigation of bioterrorism-related anthrax—Connecticut, 2001. *MMWR* 2001; 50:1077-9.
5. Brachman, P.S., & A. M. Friedlander. 1999. Anthrax. In Vaccines, Third Edition, Plotkin & Orenstein (eds.), pp. 629-637.
6. Brachman, P.S., et al., 1962. Field Evaluation of a Human Anthrax Vaccine. *Amer. J. Public Health*, 52:632-645.
7. Centers for Disease Control and Prevention. General recommendations on immunization recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1994; Vol. 43 (No. RR-1).
8. Chen, R.T., et al., 1994. The Vaccine Adverse Event Reporting System (VAERS). *Vaccine* 12(6): 542-550.

Revision: January 31, 2002

Rx Only---Federal (U.S.A.) law prohibits dispensing without a prescription.

Manufactured by
BIOPORT CORPORATION
Lansing, Michigan 48906
U.S. License No. 1260

50483-04

I. LABELING

Michigan Department of Public Health
Bureau of Laboratories

PACKAGE INSERT

ANTHRAX VACCINE, ADSORBED

DESCRIPTION OF PRODUCT

This product is prepared from microaerophilic cultures of an avirulent, non-encapsulated strain of Bacillus anthracis. The cultures are grown in a synthetic medium and elaborate the protective antigen during the growth period. The potency of this product is standardized according to the U.S. Public Health Service Regulations, Part 73: Additional Standards for Anthrax Vaccine, Adsorbed. The final product contains no more than 2.4 mg aluminum hydroxide (equivalent to 0.83 mg aluminum) per 0.5 cc dose. The preservative is 0.0025% benzethonium chloride. Formaldehyde is added as a stabilizer in a final concentration not to exceed 0.0037%.

This product should be stored at 5°C ($\pm$ 3°C). Do not freeze. Do not use after the expiration date given on the package.

RECOMMENDATIONS FOR USE

These recommendations are prepared by the Bureau of Laboratories, Michigan Department of Public Health, only for the guidance of the physician. They do not replace the experience and judgment of the physician, who should be familiar with the recent pertinent medical literature before administering any biologic preparation.

Since the risk of exposure to anthrax infection in the general population is slight, routine immunization is not recommended. Immunization with this antigen is recommended for individuals who may come in contact with imported animal hides, furs, bonemeal, wool, hair (especially goat hair), and bristles; for all personnel in factories handling these materials, and for individuals contemplating investigational studies involving Bacillus anthracis (Ref. 1).

Primary immunization consists of six subcutaneous injections of vaccine; 0.5 ml for each injection. Three injections, two weeks apart, are given first; then three more doses, six, twelve, and eighteen months after the initial injection.

If immunity is to be maintained, a booster injection of 0.5 ml of vaccine at one year intervals is recommended.

PRECAUTIONS

1. Antibody response and reactions thus far have been conducted exclusively in men and women 18 to 65 years of age. The effect of administration of the antigen in younger or older subjects as well as in pregnant women has not been studied.
2. Epinephrine solution, 1:1000 should always be available for immediate use in case an anaphylactic reaction should occur, even though such reactions are rare.

DIRECTIONS FOR USE

(Do Not Syringe-Mix With Any Other Product)

1. Use a separate heat sterilized needle and syringe (or sterile disposable needle and syringe) for each patient to avoid transmission of viral hepatitis and other infectious agents.
2. Shake the bottle thoroughly to ensure that the suspension is homogeneous during withdrawal. The rubber stopper should be treated with 2% iodine and allowed to dry before inserting the needle.
3. This preparation must be given subcutaneously after cleansing the overlying skin with an antiseptic.
4. Follow the usual precautions to avoid intravenous injection.
5. After withdrawing the needle, the injection site may be massaged briefly and gently to promote dispersal of the vaccine.
6. The same site should not be used for more than one injection of this vaccine.

CONTRAINDICATIONS

1. A history of clinical anthrax infection is an absolute contraindication to immunization with this vaccine.
2. If a person has not previously been immunized against anthrax, an injection of this product will not protect against infection following exposure to anthrax bacilli.

3. Severe systemic reactions with marked chills and fever have been reported in only a few cases over the 5 year period that this vaccine has been in use; in such instances, immunization should be discontinued
4. Any acute respiratory disease or other active infection is generally considered to be adequate reason for deferring an injection.
5. Persons receiving cortico-steroid therapy or other agents which would tend to depress the immune response may not be adequately immunized with the dosage schedule recommended. If the therapy is short termed, immunization should be delayed. If the therapy is long termed, an extra dose should be given a month or more after therapy is discontinued.

REACTIONS TO INJECTION

Mild local reactions consisting of a small zone of erythema with slight local tenderness or a small area of induration with pruritus have occurred in approximately 6 percent of all injections. Moderate local reactions have occurred after approximately one percent of injections. These generally appeared within 24 hours and subsided within 48 to 72 hours. A few subjects developed small, firm, painless nodules at the injection site which persisted for several weeks.

A small number of severe local reactions consisting of edema, moderate erythema, induration, and considerable local warmth, tenderness, and pruritus have occurred. Except for the ulceration and subsequent eschar these reactions were similar to those observed in cutaneous anthrax. Rarely, an individual demonstrated extensive edema of the arm lasting 3 to 5 days. All local reactions have been completely reversible.

Severe systemic reactions with marked chills and fever have been reported in only a few cases over the 5 year period that this vaccine has been in use for both primary and booster immunization; hence their occurrence is extremely rare (see CONTRAINDICATIONS

REFERENCE

1. Brachman, P.S. et al. Field Evaluation of a Human Anthrax Vaccine. Amer. J. Pub. Health, 52: 632-645 (1962).

Prepared by Bureau of Laboratories
Michigan Department of Public Health
Lansing, Michigan 48914
U.S. License No. 99

This vaccine is distributed by the Center for Disease Control. Inquiries should be directed to:

Center for Disease Control
Atlanta, Georgia 30333
Attention: Investigational Vaccines Activities
Laboratory Program

ANTHRAX VACCINE ADSORBED

Vial.

Dose 0.5 ml. **Contains 9 ml.**
Preserved with benzethonium chloride 0.0025%
Prepared by Bur. of Labs., Mich. Dept. of Public Health
LANSING, MICH 48914 U.S. License No. 99
F 484 **SHAKE BEFORE USING**

Lot No
Exp Date

ANTHRAX VACCINE ADSORBED

Carton

Dose 0.5 ml. Contains 9 ml.
Preserved with benzethonium chloride 0.0025%
Prepared by Bur. of Labs., Mich. Dept. of Public Health
U.S. License No. 99
F 484 SHAKE BEFORE USING

Lot No.
Exp. Date

Caution: Federal law prohibits dispensing without prescription

Keep at 5° C (±3° C)
(35.6 to 46° F)
DO NOT FREEZE
Detailed instructions inside

Prepared by Bureau of Laboratories
MICHIGAN DEPARTMENT OF PUBLIC HEALTH
Lansing, Michigan 48914

U. S. License No. 99
DISTRIBUTED FREE

F410

LEXSEE 942 F. SUPP. 19

BERLEX LABORATORIES, INC., Plaintiff, v. FOOD AND DRUG ADMINISTRATION, et al., Defendants.

Civil Action No. 96-0971 (JR)

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

942 F. Supp. 19; 1996 U.S. Dist. LEXIS 15169

October 7, 1996, Decided
October 7, 1996, FILED

DISPOSITION: [**1] Plaintiff's motion for summary judgment [# 48] DENIED. Defendants' motions to dismiss [# 36, # 39] treated as motions for summary judgment GRANTED and case DISMISSED.

CASE SUMMARY:

PROCEDURAL POSTURE: Plaintiff drug manufacturer filed a motion for summary judgment in its action against defendant United States Food and Drug Administration (FDA) and intervenor competitor drug manufacturer (competitor). The drug manufacturer sought a judgment declaring that the FDA's approval of the competitor's interferon beta product was unlawful and an order rescinding its approval. The FDA and the competitor filed cross-motions for summary judgment.

OVERVIEW: The drug manufacture was given market exclusivity of its drug under the Orphan Drug Act (Act), *21 U.S.C.S. § § 360aa-*360dd. When the FDA approved the competitor's similar drug, the drug manufacturer sought recission of its action. The competitor intervened and all parties filed motions for summary judgment. The court on review granted the cross-motions of the FDA and the competitor. Giving deference to the FDA's interpretation of its regulations, the court held that the FDA had an adequate basis upon which to consider the competitor's drug "clinically superior" to the drug manufacturer's version when it relied exclusively on a single side effect. Accordingly, it did not act arbitrarily in nullifying the drug manufacturer's orphan drug protection. The drug manufacturer had standing to complain under the Public Health Service Act (PHSA), *42 U.S.C.S. § 262,* of the approval. The record contained ample support for FDA's comparability determination and for its finding that the competitor's drug was "safe, pure and potent" as required by the PHSA. As the FDA's comparability guidance document was interpretive and not legislative, its issuance did not require notice-and-comment rulemaking.

OUTCOME: The court denied the drug manufacturer's motion for summary judgment in its action to rescind the FDA's approval of a similar drug manufactured by a competitor. The court granted the cross-motions for summary judgment by the FDA and the competitor that the FDA's actions were not arbitrary, capricious, or unlawful.

LexisNexis (TM) HEADNOTES - Core Concepts:

Administrative Law > Informal Agency ActionsGovernments > Agriculture & Food > Federal Food, Drug & Cosmetic Act

[HN1] The Orphan Drug Act, *21 U.S.C.S. § § 360aa-*360dd, permits Food and Drug Administration (FDA) approval of a drug that treats the same condition as did an original orphan drug if the FDA determines that the two drugs are not the same. A new drug is not considered the same as a previously approved drug if the new drug is "clinically superior." *21 C.F.R. § 316.3(b)(13)(ii).* A new drug is "clinically superior" if it offers greater safety in a substantial portion of the target populations. *21 C.F.R. § 316.3(b)(3)(ii).*

Governments > Agriculture & Food > Federal Food, Drug & Cosmetic Act

[HN2] *21 U.S.C.S. § 360bb*(2) provides that "orphan drugs" are drugs that treat diseases 1) affecting fewer than 200,000 persons or 2) affecting more than 200,000 person for which there is no reasonable expectation that the cost of developing and marketing the drug will be recovered from sales in the United States.

Administrative Law > Informal Agency ActionsGovernments > Agriculture & Food > Federal Food, Drug & Cosmetic Act

[HN3] Under Food and Drug Administration (FDA) regulations, an example of "greater safety" in a substantial portion of a target population is the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects. *21 C.F.R. § 316.3(b)(3)(ii)*. Even a small demonstrated diminution in adverse reactions is sufficient to allow a finding of clinical superiority of a new drug over an original orphan drug.

Administrative Law > Judicial Review > Reviewability > PreclusionAdministrative Law > Agency Rulemaking > Rule Application & Interpretation

[HN4] The court gives deference to the Food and Drug Administration's (FDA) interpretation of its regulations. The FDA's application of an interpretation in a specific case is upheld if the agency has based its decision upon relevant factors that have evidentiary support.

Administrative Law > Judicial Review > Standing

[HN5] Prudential standing to challenge an agency decision exists if the challenger is within the zone of interest to be protected or regulated by the statute. A plaintiff has no right to bring suit against an agency, however, if the plaintiff's interests are so marginally related to or inconsistent with the purposes implicit in the statute that it cannot reasonably be assumed that Congress intended to permit the suit.

Administrative Law > Judicial Review > Standing

[HN6] A plaintiff who has a competitive interest in confining a regulated industry within certain congressionally imposed limitations may sue to prevent the alleged loosening of those restrictions, even if the plaintiff's interest is not precisely the one that Congress sought to protect.

Administrative Law > Judicial Review > Standing

[HN7] The manufacturer of a "pioneer" drug has standing to sue the Food and Drug Administration (FDA) under the Public Health Service Act, *42 U.S.C.S. § 262*, for its alleged failure to enforce safety and efficacy standards against a competitor. The interests of the plaintiff and the FDA are "systematically aligned" in such a way as to promote the principal safety objective of the statute and the manufacturer is thus a "suitable challenger" for standing purposes. The pioneer drug manufacturer is well-positioned to monitor the FDA regulations implementing statutorily mandated requirements when it is their pioneer drug the generic manufacturer seeks to copy. The economic interest of such a plaintiff provides an incentive for the plaintiff to advocate the overriding necessity of ensuring public access to safe commercial drugs.

Administrative Law > Agency Rulemaking > Formal RulemakingAdministrative Law > Informal Agency ActionsGovernments > Agriculture & Food > Federal Food, Drug & Cosmetic ActAdministrative Law > Agency Rulemaking > Rule Application & Interpretation

[HN8] *42 U.S.C.S. § 262*(d)(1) of the Public Health Service Act, *42 U.S.C.S. § 262*, authorizes the Food and Drug Administration (FDA) to license biological products that meet standards designed to insure the continued safety, purity, and potency of such products. The FDA's regulations require applicants for licenses to submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency. *21 C.F.R. § 601.2(a)*. While no quantitative or measurable "standards" for safety, purity or potency exist, the regulations set out definitions of those terms that guide FDA's case-by-case determinations. *21 C.F.R. § 600.3*.

Administrative Law > Judicial Review > Reviewability > PreclusionAdministrative Law > Agency Rulemaking > Rule Application & Interpretation

[HN9] The Food and Drug Administration's (FDA) policies and its interpretation of its own regulations are paid special deference because of the breadth of Congress' delegation of authority to FDA and because of FDA's scientific expertise.

Administrative Law > Agency Rulemaking > Informal Rulemaking

[HN10] The Administrative Procedure Act requires notice-and-comment rulemaking when an agency issues new "legislative" or "substantive" rules that establish binding norms having the force of law. *5 U.S.C.S. § 553*. "Interpretive" rules, however, are expressly excused from the notice-and-comment requirements. *5 U.S.C.S. § 553*(b)(3)(A). An interpretive rule is one issued by an agency to advise the public of the agency's construction of the statutes and rules which it administers. A rule is legislative, rather than interpretive, if any one of the following four questions is answered in the affirmative: (1) whether in the absence of the rule there would not be an adequate legislative basis for agency action to confer

benefits or ensure the performance of duties; (2) whether the agency has published the rule in the Code of Federal Regulations; (3) whether the agency has explicitly invoked its general legislative authority: or (4) whether the rule effectively amends a prior legislative rule.

COUNSEL: James R. Phelps, Robert A. Dormer, A. Wes Siegner, Jr., Hyman, Phelps & McNamara, P.C., Washington, DC. Drake Cutini, Office of Consumer Litigation, U.S. Department of Justice, Washington, DC, Counsel for Defendants.

Counsel for Plaintiff: Allen R. Snyder, Robert P. Brady, Douglas A. Fellman, Gregory G. Garre, Hogan & Hartson, Washington, DC. William C. Brashares, William A. Davis, Michael B. Bressman, Mintz, Levin, Cohn, Ferris, Glovsky and Popeo, P.C., Washington, DC. Michael J. Astrue, Elan Z. Ezickson, Biogen, Inc., Cambridge, MA.

Counsel for Intervenors: Meredith Manning, U.S. Food and Drug Administration, Rockville, MD.

JUDGES: James Robertson, United States District Judge

OPINIONBY: James Robertson

OPINION:

[*21] **MEMORANDUM OPINION**

Plaintiff Berlex Laboratories, Inc. ("Berlex") manufactures Betaseron, a biological drug classified as an interferon beta product. n1 On July 23, 1993, the Food and Drug Administration approved Betaseron for the treatment of multiple sclerosis. Because it was the first interferon [**2] beta product approved for the treatment of MS, Betaseron was also given market exclusivity for seven years under the Orphan Drug Act. *21 U.S.C. § § 360aa*-360dd.

> n1 Interferons are a family of proteins in the human body that inhibit the replication of a wide spectrum of viruses and are important in the functioning of the body's immune system. The interferon beta products discussed in this opinion are produced by modifying and recombining portions of deoxyribonucleic acid (DNA) molecules and inserting the altered molecules into other cells.

Intervenor-defendant Biogen, Inc. developed an interferon beta product similar to Betaseron. On May 17, 1996, the FDA approved Biogen's product, known as Avonex, for manufacture and sale in the United States for the treatment of MS.

In this action, Berlex seeks a judgment declaring that FDA's approval of Biogen's Avonex was unlawful and an order rescinding that approval. Berlex's claims are that FDA 1) unlawfully nullified Betaseron's Orphan Drug protection upon an arbitrary [**3] and capricious finding that Avonex is "clinically superior" to Betaseron; 2) violated the Public Health Service Act, *42 U.S.C. § 262*, and regulations issued thereunder by approving [*22] Avonex without requiring the completion of full clinical trials; and 3) failed to conduct required notice-and-comment rulemaking before issuing a "comparability guidance document" that was important to the approval of Avonex.

Biogen has intervened as a defendant. Cross-motions for summary judgment were argued on September 5, 1996. This memorandum sets forth the reasons for the accompanying order granting the motions of FDA and Biogen and denying the motion of Berlex.

BACKGROUND

FDA's approval of Avonex on May 17, 1996, marked the first time FDA had approved a biological product for manufacture and sale without requiring the completion of full clinical trials on that actual product. In approving Avonex, FDA allowed Biogen to rely on the results of a clinical study of another company's interferon beta product, known as BG9015, after concluding that BG9015 was "comparable" to Avonex.

BG9015 was manufactured in Laupheim, Germany, by a joint venture owned half by Biogen and half by Rentschler Technology. [**4] This joint venture commissioned Dr. Lawrence Jacobs to do a clinical study of BG9015 in the United States beginning in 1990. In 1993, while the clinical trial was going on, the joint venture failed and went into receivership. Production of BG9015 ceased, but researchers had enough BG9015 to complete the clinical trials, which ended in 1994. AR 2, 157-58.

As early as 1991, Biogen had begun separately producing interferon beta products similar to BG9015 at a manufacturing site in Cambridge, Massachusetts. After the Biogen-Rentschler joint venture failed, Biogen sought FDA approval of a new interferon beta, known as BG9216. Rather than conduct new clinical trials of BG9216, Biogen sought to rely on the Jacobs study and sought to demonstrate to FDA that BG9216 and BG9015 were comparable. The FDA concluded that BG9216 and BG9015 were not comparable, however, and declined to consider data from the Jacobs study in connection with the application of BG9216. AR 2.

Biogen then developed the interferon beta cell line that ultimately became Avonex and submitted it for FDA approval. Although FDA had invariably required full-scale clinical trials for new biological drugs in the past, Biogen again [**5] sought to rely on the results of the Jacobs study conducted on BG9015, asserting that Avonex was comparable to BG9015. This time FDA agreed. After extensive biological, biochemical, and biophysical analyses, as well as pharmacokinetic studies in humans, FDA concluded that BG9015 and Avonex were "comparable" -- that they were "biochemically and functionally equivalent" -- and permitted the Jacobs study to be used in place of a separate clinical trial of Avonex itself. AR 2-10, 55-57.

Before Avonex could be approved for sale in the face of Betaseron's exclusivity under the Orphan Drug Act, FDA also had to make a finding that Avonex was "different" from Betaseron. FDA made that finding, basing its conclusion on the substantially less frequent occurrence of the death of skin tissue in the injection area, or injection site necrosis, associated with Avonex. n2 AR 29. FDA also noted that four percent of Avonex patients experience injection site reactions, such as swelling, redness or tenderness, compared to 85 percent of Betaseron patients. On the basis of those comparisons, FDA found Avonex "clinically superior" to Betaseron and therefore "different" for Orphan Drug Act purposes.

n2 Injection site necrosis sometimes requires surgical drainage or skin grafting for proper treatment. Concerns about injection site necrosis from Betaseron prompted a clinical report published in the New England Journal of Medicine. AR 502.

[**6]

On May 17, 1996, FDA approved Avonex "for the treatment of relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations." AR 1.

Approximately three weeks before FDA approved Avonex, it issued and published in the Federal Register a "guidance document." This document stated that FDA regulations permit the approval of biological products on the basis of "clinical data generated from a [*23] precursor product, made prior to a manufacturing change" so long as the manufacturer "can demonstrate that the precursor product is comparable to the manufactured product." FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products ("Comparability Guidance Document"), 3. FDA did not cite or refer to the "comparability guidance document" as a basis for its approval of Avonex. The principles and language embodied in the guidance document, however, were present in the document that announced FDA's approval of Avonex.

ANALYSIS

As a preliminary matter, it should be noted that this decision proceeds from an examination not only of the pleadings, [**7] but also of the administrative record. Defendants' motions have been treated as motions for summary judgment. *Marshall County Health Care Auth. v. Shalala, 300 U.S. App. D.C. 263, 988 F.2d 1221, 1226 n.5 (D.C. Cir. 1993).* Affidavits submitted by Berlex have not been considered, nor are they deemed to be part of the record of this case. See *Camp v. Pitts, 411 U.S. 138, 142-43, 36 L. Ed. 2d 106, 93 S. Ct. 1241 (1973).*

1. Elimination of Berlex's market exclusivity

Congress passed the Orphan Drug Act in 1983 to encourage the development of drugs for the treatment of rare diseases. n3 *21 U.S.C. § § 360aa-*360dd. The Act provides seven-year market exclusivity for orphan drugs and precludes the grant of FDA approval to other manufacturers of the same drug intended for treatment of the same disease. *21 U.S.C. § 360cc.* [HN1] The statute does permit FDA approval of a drug that treats the same condition as did the original orphan drug if FDA determines that the two drugs are not the same. FDA's implementing regulations provide that a new drug will not be considered the same as a previously approved drug if the new drug is "clinically superior." *21 C.F.R. § 316.3(b)(13)(ii).* [**8] The regulations provide further that a new drug is "clinically superior" if it offers "greater safety in a substantial portion of the target populations . . . ." *21 C.F.R. § 316.3(b)(3)(ii).* Applying those regulations to Avonex and relying primarily upon the disparity in the incidence of injection site necrosis caused by Betaseron (5%) and Avonex (0%), FDA concluded that Avonex was safer than Betaseron and therefore a "different" drug. AR 29, 502-03.

n3 [HN2] "Orphan drugs" are drugs that treat diseases 1) affecting fewer than 200,000 persons or 2) affecting more than 200,000 person for which there is no reasonable expectation that the cost of developing and marketing the drug will be recovered from sales in the United States. *21 U.S.C. § 360bb*(2).

Berlex challenges FDA's decision that Avonex is "clinically superior" to Betaseron. Berlex argues that it was arbitrary and capricious for FDA to rely exclusively on a single side effect when making that determination

and contends that FDA should instead have compared [**9] the "overall safety profiles" of Avonex and Betaseron.

The Orphan Drug Act is silent as to the nature of the analysis FDA must undertake when deciding whether one drug is clinically superior to another. [HN3] The regulations provide as an example of "greater safety" the elimination of "an ingredient or contaminant that is associated with relatively frequent adverse effects." *21 C.F.R. § 316.3(b)(3)(ii)*. FDA has interpreted its regulations to mean that even "a small demonstrated . . . diminution in adverse reactions may be sufficient to allow a finding of clinical superiority." *57 Fed. Reg. 62076, 62078* (Dec. 29, 1992). [HN4] That interpretation is entitled to the court's deference. *Lyng v. Payne, 476 U.S. 926, 939, 90 L. Ed. 2d 921, 106 S. Ct. 2333 (1986)*.

FDA's application of that interpretation in a specific case must be upheld if the agency based its decision upon relevant factors that have evidentiary support. *Ritter Transportation, Inc. v. ICC, 221 U.S. App. D.C. 312, 684 F.2d 86, 88 (D.C. Cir. 1982)*, cert. denied, *460 U.S. 1022, 75 L. Ed. 2d 494, 103 S. Ct. 1272 (1983)*. The substantial disparity between Avonex and Betaseron with regard to injection site necrosis was surely [**10] a factor relevant to safety, and Berlex does not challenge the sufficiency of [*24] the record evidence on that point. FDA had an adequate basis upon which to consider Avonex "clinically superior" to Betaseron, and its decision that Avonex is "different" for purposes of the Orphan Drug Act will not be disturbed.

2. Approval of Avonex without separate clinical trials

Berlex next asserts that FDA's approval of Avonex without requiring Biogen to conduct its own clinical trials contravened the Public Health Service Act ("PHSA") and FDA regulations issued thereunder. Biogen and FDA acknowledge FDA's past insistence upon clinical trials of each drug being considered for approval, but they contend that no statute or regulation requires it and submit that the use of data on "comparable" drugs is within FDA's discretion. In addition, Biogen argues that Berlex lacks standing to complain under the PHSA of the approval of a competitor's drug. The standing question, of course, must be addressed first.

a. Standing

[HN5] Prudential standing to challenge an agency decision exists if the challenger is within the "zone of interest to be protected or regulated by the statute . . . ." Association [**11] *of Data Processing Serv. Orgs. v. Camp, 397 U.S. 150, 153, 25 L. Ed. 2d 184, 90 S. Ct. 827 (1970)*. A plaintiff has no right to bring suit against an agency, however, "if the plaintiff's interests are so marginally related to or inconsistent with the purposes implicit in the statute that it cannot reasonably be assumed that Congress intended to permit the suit." *Clarke v. Securities Indus. Ass'n, 479 U.S. 388, 399, 93 L. Ed. 2d 757, 107 S. Ct. 750 (1987)*. There is no evidence suggesting that Congress created the PHSA to protect Berlex's economic interest in particular, or competition among drug manufacturers in general. Berlex's standing thus depends on whether its interests "coincide with the protected interests" of the PHSA in such a way that Berlex is a "suitable challenger" of FDA's decision. *Hazardous Waste Treatment Council v. Thomas, 280 U.S. App. D.C. 296, 885 F.2d 918, 922-23 (D.C. Cir. 1989)*.

The present action is obviously driven by Berlex's economic interest in maintaining Betaseron's market position. That motivation, however, does not deprive Berlex of standing. As the Court of Appeals recently concluded, [HN6] "a plaintiff who has a competitive interest in confining [**12] a regulated industry within certain congressionally imposed limitations may sue to prevent the alleged loosening of those restrictions, even if the plaintiff's interest is not precisely the one that Congress sought to protect." *First Nat'l Bank & Trust v. Nat'l Credit Union, 300 U.S. App. D.C. 314, 988 F.2d 1272, 1277 (D.C. Cir. 1993)*.

The question that must be resolved is whether the objectives of the PHSA are more likely to be frustrated or promoted by Berlex's claim. *Scheduled Airlines Traffic Offices, Inc. v. Department of Defense, 87 F.3d 1356, 1359 (D.C. Cir. 1996)* (citations omitted); *First Nat'l Bank & Trust, 988 F.2d at 1275* (quoting *Clarke, 479* U.S. at 397 n.12). Here, Berlex alleges that FDA has failed to comply with a statute that is focused on the safety and efficacy of new drugs.

On facts remarkably similar to those of the present case, the Third Circuit recently confirmed a drug manufacturer's standing to challenge FDA approval of a competing drug. *Schering Corp. v. FDA, 866 F. Supp. 821 (D.N.J. 1994)*, aff'd, *51 F.3d 390* (3d Cir.), cert. denied, *133 L. Ed. 2d 195, 116 S. Ct. 274 (1995)*. The district court in that case held that [HN7] the manufacturer [**13] of a "pioneer" drug had standing to sue the FDA for its alleged failure to enforce safety and efficacy standards against a competitor. The court reasoned that the interests of the plaintiff and the FDA were "systematically aligned" in such a way as to promote the principal safety objective of the statute and that the manufacturer was thus a "suitable challenger" for standing purposes. *Id. at 825*. The Third Circuit affirmed, observing that the pioneer drug manufacturer was "well-positioned to monitor the FDA regulations implementing statutorily mandated requirements . . .

when it is their pioneer drug the generic manufacturer seeks to copy." *Schering Corp. v. FDA, 51 F.3d 390, 396 (3rd Cir. 1995).* The court, in particular, emphasized [*25] that the economic interest of the plaintiff provided an incentive for the plaintiff to advocate the "overriding necessity of ensuring public access to safe commercial drugs." Id.

Berlex's interests are aligned sufficiently with those of the intended beneficiaries of the PHSA. As a manufacturer of a similar product that was recently approved, Berlex has both the expertise and the incentive to monitor FDA's actions. Berlex's challenge, whatever [**14] its merits, has required the FDA to justify its acknowledged departure from past drug approval procedures and to explain its conclusions that reliance on clinical tests of a "comparable" product will not compromise the statutory requirement of "safety, purity, and potency." *42 U.S.C. § 262*(d)(1). Berlex has standing to bring this claim under the PHSA.

b. FDA approval process

[HN8] The PHSA authorizes FDA to license biological products that "meet standards designed to insure the continued safety, purity, and potency of such products . . . ." *42 U.S.C. § 262*(d)(1). FDA's regulations require applicants for licenses to "submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed standards of safety, purity, and potency . . . ." *21 C.F.R. § 601.2(a).* No quantitative or measurable "standards" for safety, purity or potency exist. The regulations do, however, set out definitions of those terms that guide FDA's case-by-case determinations. *21 C.F.R. § 600.3.* n4

> n4 For example, the regulations define "safety" as "the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time." *21 C.F.R. § 600.3(p).*

[**15]

Neither the PHSA itself nor FDA's regulations issued under the PHSA provide that the clinical study offered to demonstrate the safety, purity and potency of a new biological product shall have been conducted on that very product. The absence of a specific provision on this point raises the now-standard question of whether the agency's view of what is "appropriate in the context of this particular program is a reasonable one." *Chevron, U.S.A., Inc. v. Natural Resources Defense Council, Inc., 467 U.S. 837, 845, 81 L. Ed. 2d 694, 104 S. Ct. 2778 (1984).* [HN9] FDA's policies and its interpretation of its own regulations will be paid special deference because of the breadth of Congress' delegation of authority to FDA and because of FDA's scientific expertise. *Lyng v. Payne, 476 U.S. 926, 939, 90 L. Ed. 2d 921, 106 S. Ct. 2333 (1986);* see *Bristol-Myers Squibb Co. v. Shalala, 923 F. Supp. 212, 216 (D.D.C. 1996).*

FDA's decision in this case to allow Biogen to rely on the clinical trials of BG9015 was based upon a reasonable interpretation of the PHSA and FDA regulations. FDA conceded that it had never before approved a new biological drug on the basis of a clinical study of a "comparable" [**16] drug, but FDA demonstrated by reference to public documents that the principle of comparability was not unknown and that, in fact, it had been previously applied in other situations. FDA argues that its extension of the comparability principle in this case reflects a reasonable interpretation of the statutory grant of its regulatory authority, particularly given the rapidly changing scientific and technological context in which FDA regulates biological products. The record contains ample support for FDA's comparability determination and for its finding that Avonex is "safe, pure and potent" as required by the statute. This court may not substitute its own judgment for that of the FDA, an agency created by Congress to address difficult scientific issues such as the one at the center of this claim.

3. Comparability Guidance Document

Berlex's third claim focuses on FDA's issuance, on April 25, 1996, of the "guidance document" that explained FDA's position on comparability. Berlex had predicted (accurately) that the guidance document would prove to be the harbinger of FDA's decision on May 17, 1996, to approve [*26] Biogen's license applications for Avonex. n5 Berlex's argument [**17] now is that the guidance document was unlawfully issued without the notice-and-comment rulemaking required by the APA.

> n5 The original complaint in this action, filed on April 26, 1996, sought to enjoin FDA from approving Avonex. Plaintiff's application for a temporary restraining order was denied on April 30, 1996.

The guidance document, which lays out FDA's policy for accepting clinical trials completed on "comparable" products, was published three weeks before FDA approved Avonex. The relationship between FDA's issuance of the guidance document and its approval of Avonex is not clear. FDA and Biogen both

point out that the guidance document was not mentioned in the administrative record. FDA's explanation -- that "the agency applied the policy described in the comparability guidance" but "did not rely on the guidance in doing so" -- is murky. FDA's Opposition to Plaintiff's Motion for Summary Judgment, 7. For purposes of this analysis it will be assumed that (1) FDA attached considerable importance to the [**18] comparability guidance document and (2) the issuance of the guidance document and the approval of Avonex were in fact related events. Those assumptions make it necessary to address Biogen's claim that the guidance document was improperly issued.

[HN10] The APA requires notice-and-comment rulemaking when an agency issues new "legislative" or "substantive" rules that establish binding norms having the force of law. *5 U.S.C. § 553; American Mining Congress v. Mine Safety & Health Admin., 302 U.S. App. D.C. 38, 995 F.2d 1106, 1109 (D.C. Cir. 1993).* "Interpretive" rules, however, are expressly excused from the notice-and-comment requirements. *5 U.S.C. § 553*(b)(3)(A). An interpretive rule is one "issued by an agency to advise the public of the agency's construction of the statutes and rules which it administers." *Shalala v. Guernsey Memorial Hosp., 131 L. Ed. 2d 106, 115 S. Ct. 1232, 1239 (1995).* In this circuit, a rule is legislative, rather than interpretive, if any one of the following four questions is answered in the affirmative:

> (1) whether in the absence of the rule there would not be an adequate legislative basis for . . . agency action to confer benefits or ensure the [**19] performance of duties,
> (2) whether the agency has published the rule in the Code of Federal Regulations,
> (3) whether the agency has explicitly invoked its general legislative authority, or
> (4) whether the rule effectively amends a prior legislative rule.

American Mining Congress, 995 F.2d at 1112.

In this case, all four questions are answered in the negative. First, as noted in the previous section of this memorandum, FDA had statutory authority to approve Avonex without requiring clinical trials. Second, the rule was not published in the Code of Federal Regulations. Third, the agency did not invoke its general legislative authority with respect to the guidance document. And fourth, the comparability guidance document did not effectively amend a legislative rule because it neither repudiates nor is inconsistent with any pre-existing FDA regulations. See *Shalala v. Guernsey Memorial Hosp., 131 L. Ed. 2d 106, 115 S. Ct. 1232, 1239 (1995); National Family Planning and Reproduction Health Ass'n, Inc. v. Sullivan, 298 U.S. App. D.C. 288, 979 F.2d 227, 235 (D.C. Cir. 1992).*

The existing FDA regulation requires the submission of "data derived from nonclinical laboratory [**20] and clinical studies." *21 C.F.R. § 601.2(a).* In the guidance document, FDA interpreted that language to include data from clinical studies completed on "comparable" biological products. Comparability Guidance Document, 3. That interpretation extended the boundaries of previous FDA actions and policies, to be sure, but it did not "run[] 180 degrees counter to the plain meaning of the regulation," as did the agency directive at issue in *National Family Planning and Reproduction Health Ass'n, Inc. v. Sullivan, 298 U.S. App. D.C. 288, 979 F.2d 227, 235 (D.C. Cir. 1992).* In National Family Planning, the Department of Health and Human Services had announced to the public that its interpretation of a regulation (concerning the provision of abortion counseling by physicians) was [*27] clear and definitive, and that interpretation was indeed upheld by the Supreme Court. Under different political leadership, the agency then issued a "directive," without notice-and-comment rulemaking procedures, that effectively reversed its earlier position. The Court of Appeals set the agency action aside, ruling that the agency had amended a legislative rule. *979 F.2d at 231-32.* In this case, by contrast, [**21] FDA's decision to rely upon the clinical trial of a "comparable" drug was not a reversal of course. It was a policy development with identifiable antecedents.

Nor has Berlex succeeded in demonstrating that the guidance document conflicts with any other FDA regulation. Berlex's assertion of potential conflicts that might arise between the comparability guidance document and other FDA regulations at some future time falls short of a showing that clear inconsistencies now exist.

Because the comparability guidance document was interpretive and not legislative, its issuance did not require notice-and-comment rulemaking.

CONCLUSION

FDA did not act unlawfully when it: 1) determined that Avonex is "clinically superior" to Betaseron; 2) approved Avonex for use by patients with MS without requiring clinical trials of Avonex; and 3) issued its comparability guidance document without notice-and-comment rulemaking. FDA's determination that Avonex is safe, pure and potent is amply supported by the record. An appropriate order accompanies this memorandum.

James Robertson

United States District Judge

October 7, 1996

ORDER

For the reasons stated in the accompanying memorandum, [**22] it is this 7th day of October, 1996,

ORDERED that plaintiff's motion for summary judgment [# 48] is **DENIED**. It is

FURTHER ORDERED that defendants' motions to dismiss [# 36, # 39] are treated as motions for summary judgment and **GRANTED** and this case is **DISMISSED**.

James Robertson

United States District Judge

Dated: May 9, 2000.

John L. Williams,

Director, Procurement and Grants Office, Centers for Disease Control and Prevention (CDC).

[FR Doc. 00–12107 Filed 5–12–00; 8:45 am]

BILLING CODE 4163–18–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 00N–1219]

Biological Products; Bacterial Vaccines and Related Biological Products; Implementation of Efficacy Review; Proposed Order

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is issuing a proposed order to accept the conclusions and recommendations of advisory review panels concerning the safety, effectiveness, and labeling of certain bacterial vaccines and related biological products that were previously classified into Category IIIA (remaining on the market pending further studies in support of effectiveness). On the basis of the advisory review panel findings, FDA is proposing to reclassify the relevant Category IIIA products into Category I (safe, effective, and not misbranded) or Category II (unsafe, ineffective, or misbranded). This action is being taken under the reclassification procedures.

DATES: Submit written comments on this proposed order and the reclassification of products should be submitted by August 13, 2000. Data and information submitted to FDA in connection with these reclassified products will be made publicly available after June 14, 2000. Comments concerning confidentiality should be received by FDA before June 14, 2000.

ADDRESSES: Submit written comments on the proposed order to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Comments may also be submitted electronically at www.fda.gov/ohrms/dockets. Copies of the reports from the Vaccines and Related Biological Products Advisory Committee (April 1984) and the Panel on Review of Allergenic Extracts (December 1983) can be obtained from the Office of Communication, Training and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448. Requests for copies that are accompanied by a self-addressed adhesive label will assist that office in processing your requests. The documents may also be obtained by mail either by calling the CBER Voice Information System at 1–800–835–4709 or 301–827–1800 or by submitting a request electronically at www.CBER_INFO@CBER.FDA.GOV, or by fax by calling the FAX Information System at 1–888–CBER–FAX or 301–827–3844.

FOR FURTHER INFORMATION CONTACT: Steven Falter, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–827–6343.

SUPPLEMENTARY INFORMATION:

I. Background

A. The Review Procedures (21 CFR 601.25)

On July 1, 1972, responsibility for regulating biological products under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) was transferred from the National Institutes of Health to FDA (37 FR 12865, June 29, 1972). Section 351 of the PHS Act provides statutory authority to license biological products. In 1973, FDA established a procedure to review the safety, effectiveness, and labeling of all biological products licensed prior to July 1, 1972 (38 FR 4319, February 13, 1973). This process was eventually codified in § 601.25 (21 CFR 601.25) (38 FR 32048 at 32052, November 20, 1973). Under § 601.25, the Commissioner of Food and Drugs assigned responsibility for the initial review of all biological products licensed prior to 1972 to nine independent advisory review panels. These panels consisted of qualified nonFDA experts in order to ensure public confidence in, and objectivity of the reviews. Each of the advisory review panels was assigned to review a specific category of biological products.

In the **Federal Register** of June 19, 1974 (39 FR 21176), FDA eliminated three previously planned panels (The Panel on Review of In Vitro Diagnostic Reagents; The Panel on Review of Immune Serums, Antitoxins, and Antivenins; and the Panel on Review of Miscellaneous Biological Products) and reassigned the review of the biological products originally intended for review by these three panels to the remaining six advisory review panels: The Panel on Review of Bacterial Vaccines and Toxoids with Standards of Potency, The Panel on Review of Bacterial Vaccines and Bacterial Antigens with "no U.S. Standards of Potency," the Panel on Review of Skin Test Antigens, The Panel on Review of Allergenic Extracts, The Panel on Review of Viral and Rickettsial Vaccines, and the Panel on Review of Blood and Blood Derivatives. The advisory review panels for bacterial vaccines and bacterial antigens with "no U.S. standard of potency," bacterial vaccines and toxoids with standards of potency, and skin test antigens reviewed the products that are the subject of this notice.

Under the review and classification procedures specified in § 601.25, each advisory review panel was charged with preparing a report to the agency that: (1) Evaluated the safety and effectiveness of the biological product; (2) reviewed the labeling of the biological product; and (3) advised FDA on which biological products under review were safe, effective, and not misbranded. Each advisory review panel report was to include a statement classifying the products into Category I, Category II, or Category III. Category I designated those biological products determined to be safe, effective, and not misbranded. Category II designated those biological products determined to be unsafe, ineffective or misbranded. Category III designated those biological products that did not fall within either Category I or Category II because of insufficient data and for which further testing was therefore required. Category III products were assigned to one of two subcategories. Category IIIA products were those that would be permitted to remain on the market pending the completion of further studies. Category IIIB products were those for which the panel report recommended license revocation on the basis of the panel's assessment of potential risks and benefits.

After reviewing the conclusions and recommendations of the panels, FDA would publish in the **Federal Register** a proposed order containing: (1) A statement designating the biological products reviewed into Categories I, II, IIIA or IIIB; (2) a description of the testing necessary for Category IIIA biological products; and (3) the complete panel report. Under the proposed order, FDA would revoke the licenses of those products designated into Category II and Category IIIB. After reviewing public comments, FDA would publish a final order on the matters covered in the proposed order.

B. Section 601.25 and Products Subject to This Proposed Order

1. The Panels on Review of Skin Test Antigens and Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency"

In the **Federal Registers** of September 30, 1977 (42 FR 52674), and November 8, 1977 (42 FR 58266), FDA published proposals for the implementation of the efficacy reviews for skin test antigens and bacterial vaccines and antigens with "no U.S. standard of potency," respectively. These proposals were in response to the reports of The Panel on Review of Skin Test Antigens, and the Panel on Review of Bacterial Vaccines and Antigens with "no U.S. standard of potency," and contained each Panel's findings and recommendations to designate each of the products reviewed into Categories I, II, IIIA or IIIB. In these proposed orders, FDA agreed with each Panel's findings and recommendations, and in accordance with §§ 601.5(b) (21 CFR 601.5(b)) and 601.25(f)(3), notified manufacturers of those products identified for classification into Category II or Category IIIB of the agency's intent to publish a notice of an opportunity for hearing to revoke the licenses for these products. Additionally, in accordance with § 601.25(f)(3), FDA proposed that those products identified for classification into Category IIIA remain on the market and that their licenses remain in effect on an interim basis pending completion of scientifically sound studies to demonstrate efficacy in humans. In the **Federal Registers** of October 28, 1977 (42 FR 56800), and December 9, 1977 (42 FR 62162), under 21 CFR 12.21(b), FDA published notices of opportunity to request hearings, submit additional data, and comment on the proposed revocation of licenses for certain skin test antigens and bacterial vaccines and antigens with "no U.S. standard of potency," respectively. Through these FR notices, manufacturers of skin test antigens and bacterial vaccines and antigens with "no U.S. standard of potency" previously identified for classification into Category II or Category IIIB were offered an opportunity for a hearing on the proposed revocation of existing licenses for products placed in Category II or IIIB.

The manufacturers of skin test antigens and bacterial vaccines and antigens with "no U.S. standard of potency," whose products were identified as Category II or Category IIIB either: (1) Did not request a hearing, (2) requested a hearing but submitted no data, (3) requested a hearing and submitted additional data that justified reclassification of products without the need for the requested hearing, or (4) requested that their product licenses be revoked. Therefore, FDA published in the **Federal Register** of October 27, 1978 (43 FR 50247), a notice reclassifying one bacterial vaccine with "no U.S. standard of potency" from Category IIIB into Category IIIA, and revoking the product licenses for the remaining bacterial vaccines and bacterial antigens with "no U.S. standard of potency" classified in Category II or Category IIIB. In the **Federal Register** of October 27, 1978, FDA also published a notice reclassifying certain skin test antigens from Category IIIB into Category IIIA, and revoking the product licenses for the remaining skin test antigens classified as Category IIIB (43 FR 50250).

2. The Panel on Review of Bacterial Vaccines and Toxoids with Standards of Potency

In the **Federal Register** of December 13, 1985 (50 FR 51002), FDA published a proposed rule containing the implementation of the efficacy review for bacterial vaccines and toxoids with standards of potency (hereinafter referred to as the December 1985 proposal). The December 1985 proposal was in response to the report of The Panel on Review of Bacterial Vaccines and Toxoids with Standards of Potency, and contained the Panel's findings and recommendations to designate each of the products reviewed into Categories I, II, IIIA or IIIB. In the December 1985 proposal, FDA: (1) Disagreed with the Panel's findings and recommendations to classify some products as Category IIIB, and reclassified these products into Category I, (2) agreed with the Panel's recommendations to classify the remaining products into Category II or Category IIIB, and (3) provided notice that licenses for several products recommended by the Panel for classification into Category IIIB and the license for the single product recommended for classification into Category II were voluntarily revoked at the request of the manufacturers prior to publication of the proposed order.

Subsequent to the Panel's review but prior to the publication of the December 1985 proposal, the regulations were revised and reclassification review procedures were established under § 601.26 (21 CFR 601.26) (47 FR 44062 at 44071, October 5, 1982). Therefore, the classification process for bacterial vaccines and toxoids with standards of potency will be completed in accordance with § 601.26 as described below.

II. Reclassification Procedures (Section 601.26)

A. The Reclassification Process

In 1982, FDA issued a regulation that established procedures to reclassify those products in Category IIIA into either Category I or Category II (47 FR 44062, October 5, 1982). This regulation was codified in § 601.26. According to § 601.26, Category IIIA products that would be reclassified included: (1) Products that an advisory panel had recommended be assigned to Category IIIA, (2) products that FDA had proposed to place in Category IIIA, or (3) products for which FDA had issued a final order reclassifying the products into Category IIIA. Under § 601.26, advisory review panels would review all Category IIIA products and make recommendations concerning each product's reclassification. During the advisory panel reclassification review process, interested persons were permitted to attend meetings, appear before the advisory review panels, and submit data to the panels for review. The advisory review panels would then submit a report to FDA that recommended the reclassification of each Category IIIA product into either Category I or II. After reviewing the conclusions and recommendations of the advisory panels, FDA would publish in the **Federal Register** a proposed order containing the following: (1) A statement designating the products as Category I or Category II, (2) a notice of availability of the full panel report, (3) a proposal to accept or reject the findings of the advisory review panels, and (4) a statement identifying those products that FDA proposes should be permitted to remain on the market because of a compelling medical need and no suitable alternative exists as described in § 601.26(d)(4).

B. Section 601.26 and the Products Subject to this Proposed Order

FDA assigned the reclassification review of bacterial vaccines and related biological products previously classified into Category IIIA by FDA based on the recommendations of the Panel on Review of Bacterial Vaccines and Antigens with "no U.S. Standard of Potency" and the Panel on Review of Skin Test Antigens to the Vaccines and Related Biological Products Advisory Committee (VRBPAC). FDA also assigned the reclassification review of vaccines and related biological products previously recommended for classification into Category IIIA by the Panel on Review of Bacterial Vaccines and Toxoids with Standards of Potency to the VRBPAC. In accordance with the

procedures specified above, FDA is notifying the public through this **Federal Register** notice of the agency's proposed reclassification of the Category IIIA products reviewed by the VRBPAC.

This proposed order contains notice of FDA's intent to revoke the licenses of certain vaccines and related biological products, listed below, that FDA proposes, based on VRBPAC recommendations, to reclassify from Category IIIA to Category II. The public may submit comments to FDA concerning this proposed order. After the end of the comment period, if FDA determines to go forward with the license revocation proceedings, the agency will publish a notice of opportunity for hearing (NOOH) on the revocation of the license of each product in Category II. After reviewing the comments on the proposed order, FDA will issue a final order on the matters covered in the proposed order. Depending upon whether a manufacturer requests a hearing on the revocation of its biologics license, FDA may consolidate the final order with license revocations.

III. Identification of Category IIIA Products Subject to Reclassification

A. Review and Reclassification Procedures, Bacterial Vaccines and Toxoids With Standards of Potency. (Bacterial Vaccines and Toxoids with Standards of Potency, Antitoxins, and Immune Globulins)

In the December 1985 proposal, FDA identified those products that were originally recommended for classification into Category IIIA and that were now subject to review by the VRBPAC under § 601.26.

Several bacterial vaccines and toxoids with standards of potency were classified into two categories based upon their use as a primary immunogen or as a booster. For example, a vaccine product could be assigned a Category IIIA designation for use as a primary immunogen but could be designated as Category I for booster use. The classifications were different because the potency tests for diphtheria and tetanus toxoids were found suitable for determining the acceptability of the toxoids for booster use, but not for determining the acceptability of the toxoids for use in primary immunization. Products listed in Table 1 were those recommended by the Panel on Review of Bacterial Vaccines and Toxoids With Standards of Potency for classification into Category I when used for booster immunization, and classification into Category IIIA when used for primary immunization. In addition, two immune globulins were recommended by the Panel for classification into Category IIIA (Table 2).

TABLE 1.—BACTERIAL VACCINES AND TOXOIDS RECOMMENDED FOR CLASSIFICATION IN CATEGORY I FOR BOOSTER IMMUNIZATION AND CATEGORY IIIA FOR PRIMARY IMMUNIZATION BY THE PANEL ON REVIEW OF BACTERIAL VACCINES AND TOXOIDS WITH STANDARDS OF POTENCY

Manufacturer/License Number	Product(s)
Istituto Sieroterapico Vaccinogeno Toscano (Sclavo), No. 238	Tetanus Toxoid
Lederle Laboratories, Division, American Cyanamid Co., No 17	Diphtheria and Tetanus Toxoids Adsorbed
	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed
	Tetanus and Diphtheria Toxoids Adsorbed (Adult Use)
	Tetanus Toxoid
	Tetanus Toxoid Adsorbed
Merck Sharp & Dohme, Division of Merck & Co., Inc., No. 2	Tetanus Toxoid Adsorbed
Connaught Laboratories, Inc., No. 711.	Tetanus and Diphtheria Toxoids Adsorbed (Adult Use)
	Tetanus Toxoid
	Tetanus Toxoid Adsorbed
Michigan Department of Public Health, No. 99	Diphtheria and Tetanus Toxoids Adsorbed
	Tetanus Toxoid Adsorbed
Swiss Serum and Vaccine Institute Berne, No. 21	Tetanus Toxoid Adsorbed
Wyeth Laboratories, Inc., No. 3	Diphtheria and Tetanus Toxoids Adsorbed
	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed
	Tetanus and Diphtheria Toxoids Adsorbed (Adult Use)
	Tetanus Toxoid
	Tetanus Toxoid Adsorbed

TABLE 2.—IMMUNE GLOBULINS RECOMMENDED FOR CLASSIFICATION IN CATEGORY IIIA FOR PASSIVE IMMUNIZATION BY THE PANEL ON REVIEW OF BACTERIAL VACCINES AND TOXOIDS WITH STANDARDS OF POTENCY

Manufacturer/License Number	Product(s)
Hollister-Stier, a Division of Cutter Laboratories, No. 8	Pertussis Immune Globulin (Human)
Travenol Laboratories Inc., Hyland Therapeutics Division, No. 140	Pertussis Immune Globulin (Human)

B. Review and Reclassification Procedures, Bacterial Vaccines and Bacterial Antigens with "No U.S. Standard of Potency"

In the **Federal Register** of January 5, 1979 (44 FR 1544), FDA issued a final rule classifying Bacterial Vaccines and Bacterial Antigens with "no U.S. standard of potency" based on the review and recommendation of the Panel on Review of Bacterial Vaccines and Bacterial Antigens with "no U.S. Standard of Potency." In the January 1979 final rule, FDA classified the products listed in Table 3 into Category IIIA.

TABLE 3.—BACTERIAL VACCINES AND BACTERIAL ANTIGENS WITH "NO U.S. STANDARD OF POTENCY" CLASSIFIED INTO CATEGORY IIIA

Manufacturer/License Number	Product(s)
Eli Lilly and Co., No. 56	Respiratory UBA (UBA–32) [1]
Hollister-Stier, a Division of Cutter Laboratories, No. 8	Bacterial Vaccines Mixed Respiratory (MRV or MRVI; licensed as Polyvalent Bacterial Vaccines with No U.S. Standard of Potency) Bacterial Vaccines for Treatment, Special Mixtures containing only the following organisms—*Staphylococcus* (*aureus* and *albus*), *Streptococcus* (*viridans* and *nonhemolytic*), *Di plococcus pneumoniae*, *Neisseria catarrhalis*, *Klebsiella pneumoniae*, *Haemophilus influenzae* (licensed as Polyvalent Bacterial Vaccines with No U.S. Standard of Potency)
Sclavo Istituto Sieroteraico Vaccinogeno Toscano (Sclavo), No. 238	Staphylococcus Toxoid [2]
Lederle Laboratories Division, No. 17	Staphylococcus Toxoid; Formalinized: Dilution No. 1, Dilution No. 2; Digest-Modified [3]
Delmont Laboratories, Inc., No. 299	Polyvalent Bacterial Antigens with "No U.S. Standard of Potency" Staphage Lysate (SPL) Types I and III [4]

[1] Respiratory UBA, Lilly, was not reviewed by the Reclassification Committee. However, the license to manufacture this product was revoked at the request of the manufacturer on December 2, 1985. Therefore, no further regulatory action was required.
[2] The license for Staphylococcus Toxoid, Sclavo, was revoked on May 9, 1979, at the request of the manufacturer and was not, therefore, subject to reclassification.
[3] The licenses for Staphylococcus Toxoid, Lederle Laboratories, were revoked on April 3, 1979, and May 21, 1980, at the request of the manufacturer and were not, therefore, subject to reclassification.
[4] This product was originally placed in Category IIIB. However, additional data submitted by the firm were found to be adequate to reclassify the product from Category IIIB to IIIA (43 FR 50247, October 27, 1978).

C. Review and Reclassification Procedures, Skin Test Antigens

In the **Federal Register** of July 10, 1979 (44 FR 40284), FDA issued a final rule classifying skin test antigens into category IIIA based on the review and recommendations of the Panel on Review of Skin Test Antigens (hereinafter referred to as the July 1979 final rule. The July 1979 final rule placed the products listed in Table 4 into Category IIIA.

TABLE 4.—SKIN TEST ANTIGENS CLASSIFIED INTO CATEGORY IIIA

Manufacturer/License Number	Product
Michigan Department of Public Health, No. 99	Histoplasmin [1]
Hollistier-Stier, a Division of Cutter Laboratories, No. 8	Coccidioidin [2]
Iatric Corp., No. 416	Coccidioidin [3]
Massachusetts Public Health Biologic Laboratories, No. 64	Diphtheria Toxin for Schick Test [4]
Eli Lilly & Co., No. 56	Mumps Skin Test Antigen

[1] The license for Histoplasmin, Michigan Department of Public Health was revoked at the request of the manufacturer on July 30, 1979. Therefore, the product was not subject to reclassification.
[2] The license for Coccidiodin, Hollistier-Stier, was revoked at the request of the manufacturer on November 1, 1979. Therefore, the product was not subject to reclassification.
[3] Coccidiodin, Iatric, was not reviewed by the Reclassification Panel. However, the license for Coccidiodin was revoked on June 25, 1997, at the request of the manufacturer. Therefore no further regulatory action on this product is required.
[4] Diphtheria Toxin for Schick Test manufactured by Massachusetts Public Health Biologic Laboratories was reclassified from Category IIIA into Category I by FDA in a FEDERAL REGISTER publication of October 16, 1981 (46 FR 51036). This action was based on the manufacturer's completion of studies and submission of data to FDA supporting the effectiveness of the product. Accordingly, the product was not subject to reclassification.

IV. Proposed Reclassification of Category IIIA Products

In the December 1985 proposal, FDA assigned the VRBPAC, as an advisory review panel, to review all bacterial vaccines and related biological products previously classified into Category IIIA or recommended for classification into Category IIIA, and to reclassify such products into either Category I (safe, effective, and not misbranded) or Category II (unsafe, ineffective, or misbranded).

The VRBPAC reviewed bacterial vaccines and related biological products in Category IIIA, including those products in Category IIIA for a particular use and in Category I for another use. For example, the Committee reviewed the use of vaccines for primary immunization, but did not review their use for booster immunization in cases where they were classified in Category IIIA and Category I, respectively. The VRBPAC reviewed all Category IIIA products, that FDA assigned to it, for effectiveness only; all such products were previously found to be safe.

The VRBPAC held reclassification meetings on January 20 and 21, 1983, June 9 and 10, 1983, and September 19, 1983, and submitted a final report, dated April 1984, to FDA.

The VRBPAC's recommendations for product classifications and FDA's responses to the recommendations are discussed below.

A. Category I. (Biological Products Determined to be Safe and Effective and Not Misbranded)

Products recommended by the VRBPAC for classification into Category I for both primary and booster immunization are listed in Table 5.

TABLE 5.—PRODUCTS RECOMMENDED BY THE VRBPAC FOR CATEGORY I CLASSIFICATION FOR BOTH PRIMARY AND BOOSTER IMMUNIZATION

Manufacturer/License Number	Product(s)
Aventis Pasteur, Inc., No. 1277	Tetanus and Diphtheria Toxoids Adsorbed (Adult Use) Tetanus Toxoid Adsorbed[1]
Lederle Laboratories Division, American Cyanamid Co., No. 17	Diphtheria and Tetanus Toxoids Adsorbed Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Tetanus and Diphtheria Toxoids Adsorbed (Adult Use) Tetanus Toxoid Tetanus Toxoid Adsorbed
Wyeth Laboratories, Inc., No. 3	Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed Tetanus Toxoid Adsorbed

[1] The licenses for these products were transferred from Connaught Laboratories, Inc., No. 711, to Aventis Pasteur Inc., No. 1277 on December 9, 1999.

After reviewing previously submitted data and additionally submitted data for the products listed in Table 5, the VRBPAC concluded that these products are effective for primary immunization and for booster immunization. The Committee recommended that these products be classified as Category I.

FDA agrees with the VRBPAC's conclusions and recommendations concerning the Category I classifications of the products listed in Table 5. FDA therefore proposes to designate these products as safe, effective, and not misbranded, and to accept the VRBPAC's findings.

In its final report to FDA, the VRBPAC recommended that three products be classified into Category II for primary immunization, and Category I for booster immunization. This recommendation was based on the fact that the manufacturers of these products did not submit data demonstrating the efficacy of the products for use in primary immunization. However, subsequent to the completion of the VRBPAC's review and submission of the final report to FDA, additional data were submitted to the agency in support of the efficacy of the use of these products for primary immunization. Therefore, FDA proposes to reclassify these products as safe, effective, and not misbranded for both primary and booster immunization. These products are listed in Table 6 followed by a detailed discussion.

TABLE 6.—PRODUCTS RECOMMENDED BY THE VRBPAC FOR CATEGORY II CLASSIFICATION FOR PRIMARY IMMUNIZATION AND CATEGORY I FOR BOOSTER IMMUNIZATION, WHICH FDA PROPOSES TO CLASSIFY INTO CATEGORY I FOR BOTH PRIMARY AND BOOSTER IMMUNIZATION

Manufacturer/License Number	Product(s)
Wyeth Laboratories, Inc., No. 3	Tetanus Toxoid Diphtheria and Tetanus Toxoids Absorbed
Swiss Serum and Vaccine Institute Berne, No. 21	Tetanus Toxoid Adsorbed

The VRBPAC in its initial reclassification report placed Tetanus Toxoid and Diphtheria and Tetanus Toxoids Adsorbed, manufactured by Wyeth Laboratories, Inc. (Wyeth), in Category II for primary immunization because no additional data had been submitted. However, on April 4, 1986, Wyeth submitted clinical study reports to FDA regarding the use of both Tetanus Toxoid and Diphtheria and Tetanus Toxoids Adsorbed for primary immunization. These data were reviewed by FDA and medical consultants from the VRBPAC. Both FDA and the VRBPAC consultants agreed that the clinical study data submitted by Wyeth supported reclassification of Wyeth's Tetanus Toxoid and Diphtheria and Tetanus Toxoids Adsorbed into Category I for both primary and booster immunization. Therefore, FDA proposes to designate these products as safe, effective, and not misbranded.

The VRBPAC in its initial reclassification report also placed Tetanus Toxoid Adsorbed, manufactured by Swiss Serum and Vaccine Institute Berne in Category II because no efficacy data had been submitted. However, on June 18, 1991, FDA approved a license supplement from Swiss Serum and Vaccine Institute Berne to update the firm's product license application for Tetanus Toxoid Adsorbed. The supplement included serologic data in support of primary immunization.

B. Category I for Booster Immunization and Category II for Primary Immunization. (Biological Products Determined to be Safe and Effective and Not Misbranded When Indicated for Booster Use Only)

Products recommended by the VRBPAC for classification in Category I for booster immunization and Category II for primary immunization are listed in Table 7.

TABLE 7.—PRODUCTS RECOMMENDED BY THE VRBPAC FOR CLASSIFICATION IN CATEGORY I FOR BOOSTER IMMUNIZATION AND CATEGORY II FOR PRIMARY IMMUNIZATION

Manufacturer/License Number	Product(s)
Aventis Pasteur, Inc., No. 1277	Tetanus Toxoid[1]
Merck Sharp & Dohme, Division of Merck & Co., No. 2	Tetanus Toxoid Adsorbed[2]
BioPort Corp., No. 1260	Diphtheria and Tetanus Toxoids Adsorbed[3] Tetanus Toxoid Adsorbed
Istituto Sieroterapico Vaccinogeno Toscano (Sclavo), No. 238	Tetanus Toxoid[4]

TABLE 7.—PRODUCTS RECOMMENDED BY THE VRBPAC FOR CLASSIFICATION IN CATEGORY I FOR BOOSTER IMMUNIZATION AND CATEGORY II FOR PRIMARY IMMUNIZATION—Continued

Manufacturer/License Number	Product(s)
Wyeth Laboratories, Inc., No. 3	Tetanus and Diphtheria Toxoids Adsorbed (Adult Use)

[1] The license for this product was transferred from Connaught Laboratories, Inc., No. 711, to Aventis Pasteur, Inc., No. 1277 on December 9, 1999.
[2] The license for Tetanus Toxoid Adsorbed, Merck, was revoked at the request of the manufacturer on January 31, 1986. Therefore, no further regulatory action on this product was required.
[3] The licenses for these products were transferred from Michigan Department of Public Health, No. 99, to BioPort Corp., License No. 1260 on November 12, 1998.
[4] The license for Tetanus Toxoid Vaccine, Sclavo, was revoked at the request of the manufacturer on July 27, 1993. Therefore, no further regulatory action on this product was required.

After reviewing available data, the VRBPAC recommended that the products in Table 7 be reclassified from Category IIIA to Category II for primary immunization until additional information to support effectiveness becomes available. For each of these products, either no additional information was submitted by the manufacturer or the VRBPAC found the additional information submitted was inadequate to support the effectiveness of the vaccine for primary immunization (Final Report: Addendum to Previous Panel Reports for the Reclassification of Category IIIA Biologics, April 1984).

FDA agrees with the VRBPAC's conclusions and recommendations concerning the Category II classification for primary immunization. FDA therefore proposes to designate these products as ineffective and misbranded for primary immunization and accept the VRPBAC's findings. If FDA classifies these products, under a final order, as Category II for primary immunization, it will be necessary for the agency to remove the primary immunization use from the license for each product. FDA can accomplish this if a manufacturer submits a supplement to its license that deletes the primary immunization use while maintaining the booster immunization use in the license. In order to change the license of each product in a timely manner given the required procedures of this § 601.26 reclassification process, FDA recommends that a manufacturer submit a license supplement to the agency prior to FDA publishing an NOOH on the proposed revocation of the products in Category II, which could publish as early as 30 days after the close of the comment period of this proposed order. If a manufacturer does not wish to remove the primary immunization use from its license at this time, FDA will publish an NOOH on the revocation of that use from the license after the comment period ends. In this proposed order FDA hereby offers notice of its intent to revoke the primary immunization use from the licenses of those products that have been classified as Category II for that use.

Furthermore, if a manufacturer wishes to market its product, listed in Table 7 above, for booster immunization after FDA issues a final order that classifies the product in Category II for primary immunization, the manufacturer must change its product labeling to reflect only the approved booster immunization use. Therefore, FDA is proposing that the container and package labels and the package insert include the statement "For Booster Use Only". This statement should be placed immediately following the proper name of the product and in the same size type print as the proper name. Also, any labeling references for use as a primary immunogen should be deleted. To make such a labeling revision, a manufacturer should submit a Changes Being Effected (CBE) supplement to their license in accordance with 21 CFR 601.12(c)(5) and (f)(2). FDA suggests that a manufacturer submit its labeling supplement in a timely manner so that the manufacturer may be able to market its product with appropriate labeling after a final order classifying the product in Category II for primary immunization.

C. Category II. (Biological Products Determined to be Unsafe, Ineffective or Misbranded)

The VRBPAC and the Panel on Review of Allergenic Extracts recommended that the following products listed in Table 8 be reclassified into Category II.

TABLE 8.—PRODUCTS RECOMMENDED BY THE VRBPAC AND THE PANEL ON REVIEW OF ALLERGENIC EXTRACTS FOR CATEGORY II CLASSIFICATION

Manufacturer/License Number	Product(s)
Hollister-Stier Laboratories LLC, No. 1272	Polyvalent Bacterial Vaccines with "No U.S. Standard of Potency" (Bacterial Vaccines Mixed Respiratory (MRV or MRVI, Bacterial Vaccines for Treatment, Special Mixtures) [1]
Delmont Laboratories, Inc., No. 299	Polyvalent Bacterial Antigens with "No U.S. Standard of Potency" (Staphage Lysate)
Eli Lilly and Company, No. 56	Mumps Skin Test Antigen [2]
Hollister-Stier, a Division of Cutter Laboratories, No. 8	Pertussis Immune Globulin (Human) [3]
Travenol Laboratories, Inc., Hyland Therapeutics Division, No. 140	Pertussis Immune Globulin (Human) [4]

[1] The licenses for these products were transferred from Bayer, Inc. No. 8 (formerly Hollister-Stier, a Division of Cutter Laboratories, No. 8), to Hollister-Stier, LLC, No. 1272 on June 2, 1999. These products were reviewed by the Panel on Review of Allergenic Extracts.
[2] The license for Mumps Skin Test Antigen, Lilly, was revoked on December 2, 1985, at the request of the manufacturer. Therefore no further regulatory action on this product was required.
[3] The license for Pertussis Immune Globulin, Hollistier-Stier, was revoked on August 18, 1988, at the request of the manufacturer. Therefore no further regulatory action on this product was required.
[4] The licenses for Pertussis Immune Globulin, Travenol, were revoked on April 9, 1982, and July 27, 1995, at the request of the manufacturer. Therefore no further regulatory action on this product was required.

1. Staphage Lysate

The original Panel on Review of Bacterial Vaccines and Bacterial Antigens with "no U.S. Standard of Potency," reviewed SPL manufactured by Delmont Laboratories, Inc. (Delmont). This Panel recommended that SPL be placed in Category IIIB, and that the license be revoked because: (1) There was no evidence of efficacy; and (2) if SPL was to be recommended for use as a stimulator of cell mediated immunity, either specific or general, this new "function" would require evaluation as a new biological product.

In 1978, Delmont requested a hearing in response to initiation of revocation proceedings and submitted information resulting in reclassification of SPL from Category IIIB to Category IIIA (43 FR 50247). Following this reclassification and prior to the meeting of the VRBPAC in January 1983, Delmont submitted additional information concerning SPL to the VRBPAC. This information consisted of a series of letters from physicians and patients of a testimonial nature supporting the effectiveness of SPL. These letters were accompanied by several reprints and exhibits of uncontrolled case reports and papers regarding the effectiveness and use of SPL in a variety of clinical conditions ranging from warts to hidradenitis suppurativa (HS), to chronic and progressive disorders such as multiple sclerosis (MS) and Crohn's disease.

The VRBPAC reviewed the information that Delmont submitted for the use of SPL in the treatment of the conditions described above. In addition, the VRBPAC reviewed data regarding the nonspecific stimulation of the immune response in animals. The VRBPAC noted that the information from the completed studies that were submitted indicated that the studies were insufficiently designed to support claims of SPL's effectiveness for treatment of warts, MS, Crohn's disease or nonspecific stimulation of the immune response. At the time of the VRBPAC meeting in 1983, the committee noted that two controlled trials for the use of SPL in treatment of recurrent furunculosis and HS were either in the recruitment phase or in progress. The VRBPAC noted that it would likely take additional time for the sponsors to complete these trials. However, the VRBPAC concluded that "it could not reasonably continue to defer recommendations on the classification of SPL owing to uncertainty when the two existing controlled trials would be completed, and uncertainty as to whether the results, when finally presented, would be clearly interpretable, owing to lack of comparability among patient groups" (VRPBAC Final Report: Addendum to Previous Reports for the Reclassification of Category IIIA Biologics, April 1984).

As a result of its review, the VRBPAC found that it was not able to determine that there was substantial evidence of efficacy for SPL. In its final report to the agency submitted in April of 1984, the VRBPAC recommended that SPL be placed in Category II and that"licensure be revoked until additional data to support its reclassification became available."

2. Polyvalent Bacterial Vaccines with "no U.S. Standard of Potency"

Product licenses for Polyvalent Bacterial Vaccines with "no U.S. Standard of Potency," (MRV, MRVI, and Bacterial Vaccines for Treatment, Special Mixtures) manufactured by Hollister-Stier, Division of Cutter Laboratories, were transferred to Miles Laboratories, Inc., on February 18, 1983, were transferred to Bayer, Inc. on May 24, 1995, and were again transferred to Hollister-Stier LLC on June 2, 1999. The original Panel on Review of Bacterial Vaccines and Antigens recommended that these products (MRV, MRVI, and Bacterial Vaccines for Treatment, Special Mixtures) be classified as Category IIIA and could remain on the market, and their license remain in effect on an interim basis provided that: (1) Group A streptococcal organisms and their derivatives, where present, were removed, and (2) satisfactory potency standards were developed and acceptable data based on scientifically sound studies which demonstrated efficacy in humans be submitted to FDA. At the time the agency established the § 601.26 reclassification panels, FDA, based on a recommendation of the VRBPAC, referred these three products to the Panel on Review of Allergenic Extracts for reclassification based on the products' attributed mode of action.

The Panel on Review of Allergenic Extracts (the Allergenics Panel) held reclassification meetings on November 19 and 20, 1982, February 18 and 19, 1983, and June 3 and 4, 1983, and a final report was submitted to FDA in December of 1983. In this report, the Allergenics Panel noted that the manufacturer had removed group A streptococcal organisms from MRV, MRVI, and Bacterial Vaccines, Special Mixtures, and had initiated preliminary studies as recommended by the original Panel. However, the Allergenics Panel found that "there has been no better definition of indications for the use of this product. Neither are there recognizable criteria for selection of patients or dosage. No double-blinded controlled studies have been performed or started since the original Panel made its recommendations in 1977" (Food and Drug Administration Panel on Review of Allergenic Extracts Category IIIA Reclassification, Final Report, December 1983). Based on the lack of efficacy studies submitted in support of these products, the Allergenics Panel recommended that these products be reclassified into Category II for both diagnosis and immunotherapy.

FDA agrees with the conclusions and recommendations of the VRBPAC to reclassify SPL into Category II. FDA therefore proposes to designate SPL as ineffective and misbranded and to accept the findings of the VRBPAC concerning SPL. FDA also agrees with the conclusions and recommendations of the Panel on Review of Allergenic Extracts to reclassify Hollister-Stier LLC's Polyvalent Bacterial Vaccines with "no U.S. Standard of Potency" (MRV, MRVI, and Bacterial Vaccines for treatment, Special Mixtures) into Category II. FDA proposes to designate Polyvalent Bacterial Vaccines with "no U.S. Standard of Potency" (MRV, MRVI, and Bacterial Vaccines for treatment, Special Mixtures) as ineffective and misbranded, and FDA proposes to accept the findings of the Panel on Review of Allergenic Extracts.

In this proposed order FDA hereby offers notice of its intent to revoke the licenses of SPL and Polyvalent Bacterial Vaccines with "no U.S. Standard of Potency" (MRV, MRVI, and Bacterial Vaccines for treatment, Special Mixtures) as Category II products. After the end of the comment period for this proposed order, FDA will subsequently issue a notice of opportunity for a hearing on the revocation of the license of both SPL and Polyvalent Bacterial Vaccines with "no U.S. Standard of Potency" (MRV, MRVI, and Bacterial Vaccines for treatment, Special Mixtures).

Section 601.26(d)(4) requires FDA to publish in a proposed order, concerning Category IIIA reclassification, a statement identifying those products that the agency proposes should be permitted to remain on the market pending further testing because there is a compelling medical need and no suitable alternative. No such products were identified by the VRBPAC for the purposes of this proposed order.

V. Availability of Reports and Public Comments

In accordance with § 601.26(d)(2), FDA is announcing the availability of the final reports of the Vaccines and Related Biological Products Advisory

Committee, dated April 1984, and the Panel on Review of Allergenic Extracts, dated December 1983, that are the subject of this proposed order. Copies of these reports can be obtained from the Office of Communication, Training and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448. By sending a self-addressed adhesive label, you will assist that office in processing your requests more quickly. The documents may also be obtained by mail by calling the CBER Voice Information System at 1–800–835–4709 or 301–827–1800, or by fax by calling the FAX Information System at 1–888–CBER–FAX or 301–827–3844, or by mail by contacting CBER electronically at www.CBER__INFO@CBER.FDA.GOV.

Interested persons may, on or before August 13, 2000 submit written comments regarding this proposal to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Two copies of any comments should be submitted, except that individuals should submit one copy. Comments may also be submitted electronically at www.fda.gov/ohrms/dockets. Comments should be identified with the docket number found in brackets in the heading of this document. Data and information submitted to FDA that fall within the confidentiality provisions of 18 U.S.C. 1905, 5 U.S.C. 552(b), or 21 U.S.C. 331(j) are not available for public disclosure. Consistent with the provisions of § 601.25(b), when FDA publishes this proposed order and the Reclassification Committee's reclassification findings, data and information submitted to FDA in connection with these reclassified products will be made publicly available after June 14, 2000, and may be viewed at the Dockets Management Branch (address above). Data and information submitted and shown to fall within the confidentiality provisions of one or more of the above statutes will not be disclosed. Comments concerning confidentiality should be received by FDA by June 14, 2000. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

After review of the public comments received in response to this proposed order and in consideration of the results of hearings, if any, FDA intends to issue in the **Federal Register** a final order announcing its final conclusions and revoking those licenses which are placed in Category II by the final order.

Dated: May 3, 2000.

Margaret M. Dotzel,

Acting Associate Commissioner for Policy.

[FR Doc. 00–12116 Filed 5–12–00; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 98E–0228]

Determination of Regulatory Review Period for Purposes of Patent Extension; Neuro Cybernetic Prosthesis (NCP®) System; Amendment

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; amendment.

SUMMARY: The Food and Drug Administration (FDA) is amending a previous determination regarding the regulatory review period for the Neuro Cybernetic Prosthesis (NCP®) System that appeared in the **Federal Register** of November 10, 1998 (63 FR 63066). FDA is amending the notice because the agency agrees with the information provided in a request from the applicant for revision of the regulatory review period (Request) (Docket No. 98E–022 8/PRC 1, dated and received on January 8, 1999).

ADDRESSES: Submit written comments and petitions to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Claudia V. Grillo, Regulatory Policy Staff (HFD–7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5645.

SUPPLEMENTARY INFORMATION: In its original application for patent term extension, the applicant claimed December 16, 1991, as the date the premarket approval application (PMA) for the Neuro Cybernetic Prosthesis (NCP®) System (PMA 910070) was initially submitted. FDA first determined that the PMA was initially submitted on January 27, 1997, because FDA records indicated that the PMA submitted on December 16, 1991, had not been filed, but an amended PMA, renumbered as PMA 970003, was the PMA for the approved product.

The applicant later claimed in its request that FDA's determination of the regulatory review period failed to take into account an approved amendment to the applicant's originally submitted PMA. Therefore, the applicant requested that the agency correct the date the PMA was initially submitted to June 1, 1993, the date the approved amendment to the PMA was received by FDA.

FDA reviewed its records and confirmed that the amended PMA, received on June 1, 1993, was filed by the agency based on a threshold determination that the amended PMA was sufficiently complete to permit a substantive review. FDA later determined that additional studies were required and issued a major deficiency letter dated September 30, 1994, requesting that additional clinical studies be performed. The applicant submitted a second amendment to the PMA, which the agency received on January 27, 1997. FDA reviewed the amendment and determined that the second amendment sufficiently responded to the September 30, 1994, deficiency letter, and filed the newly amended PMA on the date of the receipt of the completed PMA, January 27, 1997. For administrative reasons, the second amendment to the PMA was considered a resubmission of the PMA, and it was assigned a new PMA number, P970003, which is the PMA number of the approved PMA for the product.

In the past, FDA has determined that the start of the approval phase began with the submission of the first filed PMA for an approved product, even if the original filed PMA was later withdrawn and filed under a new number. For this reason, FDA now accepts the date of June 1, 1993, submitted by the applicant in its request, as the date the first PMA was filed for the product and the date that the PMA was initially submitted.

Therefore, the applicable regulatory review period for the Neuro Cybernetic Prosthesis (NCP®) System is 3,237 days. Of this time, 1,730 days occurred during the testing phase of the regulatory review period, while 1,507 days occurred during the approval phase.

These periods of time were derived from the following dates, summarized from the November 10, 1998, notice and modified by this technical amendment:

1. *The date a clinical investigation involving this device was begun:* September 6, 1988.

2. *The date an application was initially submitted with respect to the device under section 515 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360e):* June 1, 1993.

3. *The date the application was approved:* July 16, 1997.

This determination of the regulatory review period establishes the maximum potential length of a patent extension. However, the U.S. Patent and Trademark Office applies several

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

52FR11123
4-7-87

[DOCKET NO. 80N-0208]

BACTERIAL VACCINES AND TOXOIDS; OPPORTUNITY FOR HEARING

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing an opportunity for a hearing on a proposal to revoke the product licenses for the bacterial vaccines and toxoids classified in Category IIIB by FDA in response to the recommendations of the Panel on Review of Bacterial Vaccines and Toxoids. The bacterial vaccines and toxoids for which FDA is proposing product license revocation are not marketed currently in their licensed form.

DATES: The licensees may submit written requests for a hearing to the Dockets Management Branch by (insert date 30 days after date of publication in the FEDERAL REGISTER), and any data justifying a hearing must be submitted by (insert date 60 days after date of publication in the FEDERAL REGISTER). Other interested persons may submit comments on the proposed revocations by (insert date 60 days after date of publication in the FEDERAL REGISTER).

ADDRESS: Written requests for hearing, data, and written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Steven F. Falter,
Center for Drugs and Biologics (HFN-364),
Food and Drug Administration,
5600 Fishers Lane,
Rockville, MD 20857,
301-295-8046.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of December 13, 1985 (50 FR 51002), FDA published the report of the Panel on Review of Bacterial Vaccines and Toxoids (the Panel) and FDA's proposed response to the Panel's recommendations. The Panel found that for 40 products the available evidence was inadequate to document the products' safety and effectiveness. In its response to the Panel's report, FDA proposed that 36 of the products be classified in Category IIIB. FDA also proposed that 4 of the products be reclassified as safe and effective because of additional evidence received after the Panel's review.

In its response to the Panel's report, FDA announced its intention to revoke the product licenses for the bacterial vaccines and toxoids classified in Category IIIB. Since the time of the Panel's review, FDA has revoked the licenses for 29 of the products at the request of the manufacturer and, therefore, further revocation procedures will be unnecessary for these 29 products. FDA's response to the Panel's report lists 24 of the products for which manufacturers requested revocation (50 FR 51106). After the

publication of the Panel's report, FDA received a request from Merck Sharp & Dohme, Division of Merck & Co., Inc., for the revocation of the product licenses for Cholera Vaccine, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, and Typhoid Vaccine, License No. 2. On January 31, 1986, FDA revoked the product licenses for these five products. In its response to the Panel's report, FDA also proposed that the following products be classified in Category IIIB:

still licensed

Diphtheria Toxoid, manufactured by Istituto Sieroterapico Vaccinogeno Toscano Sclavo, License No. 238;

not licensed

Tetanus Toxoid, manufactured by Massachusetts Public Health Biologics Laboratories, License No. 64;

not licensed still licensed

Diphtheria Antitoxin, and Diphtheria Toxoid Adsorbed, manufactured by Michigan Department of Public Health, License No. 99; and

not licensed not licensed

Diphtheria Toxoid, Diphtheria Toxoid Adsorbed, and

not licensed

Pertussis Vaccine, manufactured by Wyeth Laboratories, Inc., License No. 3.

The Panel recommended that the product license be revoked for each of the products above. The Panel made clear that its recommendations for revocation of licenses were based on administrative and procedural problems and were not judgments derived from a scientific evaluation of the products. The products listed above either have never been marketed in their licensed form or they have not been

marketed for many years. As a result, the manufacturers did not submit supportive information or submitted incomplete or outdated information for the Panel's review. Therefore, the Panel found that the data were insufficient to classify the products as safe and effective and to determine the potential benefits and risk of the products. As announced in the December 13, 1985, proposed rule, FDA agrees with the Panel's findings and recommendations concerning the bacterial vaccines and toxoids listed above. FDA proposed to classify these products in Category IIIB and, in accordance with 21 CFR 601.5 and 12.21(b), FDA is offering an opportunity for hearing. A licensee may submit a written request for a hearing to the Dockets Management Branch by (insert date 30 days after date of publication in the FEDERAL REGISTER) and any data justifying a hearing must be submitted by (insert date 60 days after date of publication in the FEDERAL REGISTER). Other interested persons may submit comments on the proposed revocation to the Dockets Management Branch by (insert date 60 days after date of publication in the FEDERAL REGISTER). The failure of a licensee to file timely written appearance and request for a hearing constitutes an election of the licensee not to avail itself of the opportunity of a hearing concerning the proposed license revocation.

FDA procedures and requirements governing a notice of opportunity for hearing, notice of appearance and request for hearing, grant or denial of hearing, and submission of data and information to justify a hearing are contained in

21 CFR Parts 12 and 601 and 21 CFR 314.200. A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that there is genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information and factual analyses in the request for a hearing that there is no genuine and substantial issue of fact that precludes the revocation of the license, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner of Food and Drugs will enter summary judgment against the licensee requesting the hearing, making findings and conclusions that justify denying a hearing.

Two copies of any submissions are to be provided to FDA except that individuals may submit one copy. Submissions are to be identified with the docket number found in brackets in the heading of this document. Such submissions, except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Public Health Service Act (sec. 351, 58 Stat. 702 as amended (42 U.S.C. 262)) and the Federal Food, Drug, and Cosmetic Act (secs. 201, 501, 502, 701, 52 Stat. 1040-1042 as amended, 1049-1051 as amended, 1055-1056 as amended (21 U.S.C. 321, 352, and 371)) and under authority delegated to the Commissioner of Food

and Drugs (21 CFR 5.10) and redelegated to the Director and Deputy Director of the Center for Drugs and Biologics (21 CFR 5.67) (see the FEDERAL REGISTER of July 29, 1985; 50 FR 30696).

Dated: 3/27/87.

MAR 27 1987

Gerald F. Meyer
Acting Deputy Director
Center for Drugs and Biologics

CERTIFIED TO BE A TRUE COPY OF THE ORIGINAL

FDC date	State	City	Airport	FDC No.	SIAP
06/27/96	ID	McCall	McCall	FDC 6/4222	NDB or GPS–A, ORIG...
07/02/96	UT	Logan	Logan-Cache	FDC 6/4430	VOR or GPS-A AMDT 6... THIS CORRECTS NOTAM IN 96–16
07/11/96	MN	Brainerd	Brainerd-Crow Wing County Regional.	FDC 6/4731	VOR or GPS RWY 30 AMDT 13...
07/12/96	NE	Lincoln	Lincoln Muni	FDC 6/4755	ILS RWY 35L, AMDT 11A...
07/12/96	NE	.....do	.....do	FDC 6/4756	ILS RWY 17R, AMDT 6A...
07/16/96	IA	Dubuque	Dubuque Regional	FDC 6/4890	VOR RWY 31, AMDT 11...
07/16/96	IA	.....do	.....do	FDC 6/4894	NDB or GPS RWY 31, AMDT 8...
07/16/96	IA	.....do	.....do	FDC 6/4895	VOR OR GPS RWY 13, AMDT 8A...
07/16/96	IA	.....do	.....do	FDC 6/4896	VOR or GPS RWY 36, AMDT 5A...
07/16/96	IA	.....do	.....do	FDC 6/4897	ILS RWY 31, AMDT 10A...
07/16/96	IA	.....do	.....do	FDC 6/4898	LOC/DME BC RWY 13, AMDT 4...
07/17/96	NY	New York	John F. Kennedy Intl	FDC 6/4930	ILS RWY 4R AMDT 28B...
07/17/96	NY	.....do	.....do	FDC 6/4931	ILS RWY 13L AMDT 14A...
07/18/96	MS	Pascagoula	Trent Lott Intl	FDC 6/4967	ILS RWY 17, ORIG...
07/18/96	NY	New York	John F. Kennedy Intl	FDC 6/4979	VOR/DME or TACAN or GPS RWY 22L AMDT 4...
07/18/96	NY	.....do	.....do	FDC 6/4980	VOR or GPS RWY 4L/R AMDT 15...
07/18/96	NY	.....do	.....do	FDC 6/4983	ILS RWY 22L AMDT 22...
07/18/96	NY	.....do	.....do	FDC 6/4984	ILS RWY 31L AMDT 9...
07/18/96	NY	.....do	.....do	FDC 6/4985	ILS RWY 3IR AMDT 13...
07/19/96	GA	Columbus	Columbus Metropolitan	FDC 6/5010	ILS RWY 5, AMDT 24...
07/22/96	IL	Salem	Salem-Leckrone	FDC 6/5089	NDB or GPS RWY 18, AMDT 8...
07/22/96	NC	Raleigh-Durham	Raleigh-Durham Intl	FDC 6/5092	RADAR–1, AMDT 7...
07/23/96	IA	Charles City	Charles City Muni	FDC 6/5142	NDB–A, ORIG...
07/23/96	IA	.....do	.....do	FDC 6/5143	LOC RWY 12, ORIG– C...
07/23/96	IA	.....do	.....do	FDC 6/5144	NDB or GPS RWY 12, ORIG–C...
07/23/96	IA	Fort Madison	Fort Madison Muni	FDC 6/5139	VOR/DME RNAV or GPS RWY 34, AMDT 4...
07/23/96	IA	.....do	.....do	FDC 6/5140	VOR/DME RNAV or GPS RWY 16, AMDT 4...
07/23/96	IA	.....do	.....do	FDC 6/5141	VOR/DME or GPS–A, AMDT 6...

[FR Doc. 96–19608 Filed 7–31–96; 8:45 am]
BILLING CODE 4910–13–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 601, 620, 630, 640, 650, 660, and 680

[Docket No. 95N–310B]

Revocation of Certain Regulations; Biological Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule to remove certain biologics regulations that are obsolete or no longer necessary to achieve public health goals. These regulations were identified for removal as the result of a page-by-page review of the agency's regulations. This regulatory review is in response to the Administration's "Reinventing Government" initiative which seeks to streamline government to ease the burden on regulated industry and consumers.

EFFECTIVE DATE: August 12, 1996.

FOR FURTHER INFORMATION CONTACT:
Regarding general information on FDA's "reinventing initiative": Lisa M. Helmanis, Office of Policy (HF–26), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–3480.
Regarding biologics regulations: Annette A. Ragosta, Center for Biologics Evaluation and Research (HFM–630), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448, 301–594–3074.

SUPPLEMENTARY INFORMATION:

I. Background

On March 4, 1995, President Clinton announced plans for the reform of the Federal regulatory system as part of the Administration's "Reinventing Government" initiative. In his March 4 directive, the President ordered all Federal agencies to conduct a page-by-page review of their regulations and to "eliminate or revise those that are outdated or otherwise in need of reform." In the Federal Register of October 13, 1995 (60 FR 53480), FDA issued a notice of proposed rulemaking in which FDA proposed to remove a number of outdated or unnecessary regulations in parts 100 through 801 (21 CFR parts 100 through 801). The regulations proposed for removal apply to a variety of products regulated by FDA, including foods, drugs, veterinary drugs, biological products, and devices. Interested persons were requested when submitting comments to identify the FDA Center responsible for the regulation of the product to which the comments applied. In order to expedite matters, the final rules resulting from the line-by-line review are being issued separately by FDA Centers. FDA is issuing this final rule, which eliminates

certain regulations affecting biological products in parts 600 through 680.

II. Comments

FDA received two comments on the proposed rule that related to the biologics regulations. One comment was general in nature and urged Congress to include FDA reform as a top priority in 1996.

Congress is currently considering legislation that would affect FDA programs and procedures. FDA has testified at congressional hearings on the pending bills. The agency does not believe it would be appropriate to comment on the ongoing legislative initiatives in this rulemaking.

The agency agrees with the comment that regulatory programs and the regulations that implement them should be reviewed and revised or reformed where appropriate. FDA is currently reviewing other biologics regulations, the potential removal or revision of which involves issues of greater regulatory complexity and, based on this review, will remove or significantly revise these regulations at a later date. In addition, a number of changes to the regulations and policies affecting biological products are already underway. (See for example, "Interim Definition and Elimination of Lot-by-Lot Release for Well-Characterized Therapeutic Recombinant DNA-Derived and Monoclonal Antibody Biotechnology Products" (60 FR 63048, December 8, 1995); "Well-Characterized Biotechnology Products; Elimination of Establishment License Application" (61 FR 2733, January 29, 1996); "Changes to an Approved Application" (61 FR 2739); "Draft Guidance; Changes to an Approved Application for Well-Characterized Therapeutic Recombinant DNA-Derived and Monoclonal Antibody Biotechnology Products; Availability" (61 FR 2748); "Changes to an Approved Application; Draft Guidance; Availability" (61 FR 2749).) This final rule, "Revocation of Certain Regulations; Biological Products," is one part of the agency's efforts to create a more efficient and responsive regulatory system.

The other comment received was supportive of the proposed rule and stated that it was a good first step in reducing regulatory burden. The comment suggested the incorporation of the United States Pharmacopeia (USP) monograph system based on the Center for Drug Evaluation and Research model into the Center for Biologics Evaluation and Research's regulatory reform process.

The agency does not agree with this suggestion because biologics, for which FDA is removing additional standards from the regulations, are complex and diverse entities. Monographs for many types of biological products could become quickly outdated in the rapidly evolving field of biotechnology, as did the Additional Standards in parts 620, 630, 640, 650, 660, and 680, which this final rule is removing. Use of monographs would allow for less flexibility in the development of product specifications for complex biologicals.

III. Effective Date

As provided under 5 U.S.C. 553(d) and § 10.40(c) (21 CFR 10.40(c)), the effective date of a final rule may not be less than 30 days after the date of publication, except for, among other things, "a regulation that grants an exemption or relieves a restriction" (§ 10.40(c)(4)(i)). The final rule is effective August 12, 1996.

IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96-354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order and so is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the proposed removals have no compliance costs and do not result in any new requirements, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

V. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

21 CFR Part 620

Biologics, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 630

Biologics, Labeling.

21 CFR Part 640

Blood, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 650

Biologics.

21 CFR Part 660

Biologics, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 680

Biologics, Blood, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 601, 620, 630, 640, 650, 660, and 680 are amended as follows:

PART 601—LICENSING

1. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 513–516, 518–520, 701, 704, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381); secs. 215, 301, 351, 352 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263); secs. 2–12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451–1461).

§ 601.30 [Removed]

2. Section 601.30 *Licenses required; products for controlled investigation only* is removed.

§ 601.31 [Removed]

3. Section 601.31 *Procedure* is removed.

§ 601.32 [Removed]

4. Section 601.32 *Form of license* is removed.

PART 620—ADDITIONAL STANDARDS FOR BACTERIAL PRODUCTS

Part 620 [Removed]

5. Part 620 is removed.

PART 630—ADDITIONAL STANDARDS FOR VIRAL VACCINES

Part 630 [Removed]

6. Part 630 is removed.

PART 640—ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

7. The authority citation for 21 CFR part 640 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371); secs. 215, 351, 352, 353, 361 of the Public Health Service Act (42 U.S.C. 216, 262, 263, 263a, 264).

Subpart K [Removed and Reserved]

8. Subpart K, consisting of §§ 640.110 through 640.114, is removed and reserved.

PART 650—ADDITIONAL STANDARDS FOR DIAGNOSTIC SUBSTANCES FOR DERMAL TESTS

Part 650 [Removed]

9. Part 650 is removed.

PART 660—ADDITIONAL STANDARDS FOR DIAGNOSTIC SUBSTANCES FOR LABORATORY TESTS

10. The authority citation for 21 CFR part 660 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371); secs. 215, 351, 352, 353, 361 of the Public Health Service Act (42 U.S.C. 216, 262, 263, 263a, 264).

Subpart K [Removed]

11. Subpart K, consisting of §§ 660.100 through 660.105, is removed.

PART 680—ADDITIONAL STANDARDS FOR MISCELLANEOUS PRODUCTS

12. The authority citation for 21 CFR part 680 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371); secs. 215, 351, 352, 353, 361 of the Public Health Service Act (42 U.S.C. 216, 262, 263, 263a, 264).

13. The heading for Subpart A—Allergenic Products is removed.

Subpart B [Removed]

14. Subpart B, consisting of §§ 680.10 through 680.16, is removed.

Subpart C [Removed]

15. Subpart C, consisting of §§ 680.20 through 680.26, is removed.

Dated: July 19, 1996.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

[FR Doc. 96–19604 Filed 7–31–96; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF THE INTERIOR

Office of Surface Mining Reclamation and Enforcement

30 CFR Part 735

Grants for Program Development and Administration and Enforcement

CFR Correction

In Title 30 of the Code of Federal Regulations, parts 700 to End, revised as of July 1, 1995, on page 144, § 735.23 was inadvertently omitted. The omitted text should read as follows:

§ 735.23 Administrative procedures.

The agency shall follow administrative procedures governing accounting, payment, property and related requirements contained in Office of Management and Budget Circular No. A–102.

BILLING CODE 1505-01-D

30 CFR Part 937

Oregon

CFR Correction

In Title 30 of the Code of Federal Regulations, parts 700 to End, revised as of July 1, 1995, on page 639, § 937.772 was inadvertently omitted. The omitted text should read as follows:

§ 937.772 Requirements for coal exploration.

(a) Part 772 of this Chapter, "Requirements for coal exploration," shall apply to any person who conducts or seeks to conduct coal exploration operations.

(b) The Office shall make every effort to act on an exploration application within 60 days of receipt or such longer time as may be reasonable under the circumstances. If additional time is needed, OSMRE shall notify the applicant that the application is being reviewed, but more time is necessary to complete such review, setting forth the reasons and the additional time that is needed.

(c) Where coal exploration is to occur on State lands or the minerals to be explored are owned by the State, a mineral lease issued by the Oregon Division of Lands authorizing the coal exploration is required to be filed with the permit application.

[52 FR 13812, Apr. 24, 1987]

BILLING CODE 1505-01-D

FEDERAL COMMUNICATIONS COMMISSION

47 CFR Part 1

[MD Docket No. 96–84; DA 96–1156]

Assessment and Collection of Regulatory Fees for Fiscal Year 1996

AGENCY: Federal Communications Commission.

ACTION: Final rule.

SUMMARY: The Commission revised its Schedule of Regulatory Fees on July 1, 1996, in order to recover the amount of regulatory fees that Congress has required it to collect for fiscal year 1996. See *Report and Order in the Matter of Assessment and Collection of Regulatory Fees for Fiscal Year 1996*, Md Docket 96–84, FCC–295 (released July 5, 1996). The attached *Order* establishes the dates when these regulatory fees must be paid.

EFFECTIVE DATE: August 1, 1996.

DATES: September 30, 1996 for annual fees for Geosynchronous Space Station Licensees, Intelsat and Inmarsat Signatories, and Low Earth Orbit Satellite System Licensees. September 12, 1996, through September 20, 1996, for all other annual fee payors. Beginning on September 12, 1996, for applicants who pay fees in advance in combination with their application fee for new, renewal and reinstatement authorizations in the private wireless services.

FOR FURTHER INFORMATION CONTACT: Peter W. Herrick, Office of Managing Director at (202) 418–0443, or Terry D. Johnson, Office of Managing Director at (202) 418–0445.

SUPPLEMENTARY INFORMATION:

Adopted: July 22, 1996
Released: July 24, 1996

1. The Managing Director has determined the dates for collection of the fees adopted in the fiscal year 1996 regulatory fee proceeding. See *Assessment and Collection of Regulatory Fees for Fiscal Year 1996*, FCC–295 (released July 5, 1996), 61 FR 36629 (July 12, 1996). We are establishing collection dates as indicated below.

2. Annual regulatory fees for Geosynchronous Space Station licensees, Intelsat and Inmarsat Signatories, and Low Earth Orbit

Geary, Nathaniel

To: Butler, Jennie C
Cc: Raza, Mark; Swisher, Kathleen (CBER)
Subject: Docket No. 01P-0471/CP-1; Supporting Documents for Petition Response

This afternoon, we will hand deliver supporting documents for the Citizen Petition response. They are identified as Tabs E through K. Please place them on the docket.

Thank you.